

50  
154  
982

*National Institutes of Health*

*Annual  
Report  
of International  
Activities*

*Fiscal Year  
1982*

U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES  
Public Health Service  
National Institutes of Health



*Final 7-21-82*

*U.S.* National Institutes of Health

*Annual  
Report  
of International  
Activities*

*Fiscal Year  
1982*

Prepared by  
John E. Fogarty International Center  
for  
Advanced Study in the  
Health Sciences

U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES  
Public Health Service  
National Institutes of Health

NIH Publication No. 83-62  
July 1983

R  
850  
U54  
1982



# Foreword

On behalf of the National Institutes of Health (NIH), the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) is pleased to present this 14th Annual Report of International Activities, covering the fiscal year 1982. Edited by the FIC, but based upon reports by each of the Bureaus, Institutes, and Divisions (BID's) of the NIH, this report provides an overview of international activities for the period. These activities are essential to the furtherance of the NIH mission and fall within the purview of one or more of the BID's.

The international programs of the NIH are specifically authorized under the International Health Research Act of 1960 (P.L. 86-610) to "advance the status of the health sciences in the United States and thereby the health of the American People through cooperative endeavors with other countries in health research, research planning, and research training. . . ."The benefits of NIH international programs, however, extend far beyond our borders. Cooperative relationships that the BID's have established through their intramural and extramural programs enable foreign biomedical and behavioral research scientists to collaborate with their U.S. counterparts to discover better means for treatment, control, and--ultimately--prevention of disease worldwide.

In 1968, the Fogarty International Center was established as the focal point for the international work of the NIH. Although the number and kinds of international programs differ from Institute to Institute, the FIC is the only NIH component with an explicit international mission, which includes NIH-wide coordination of activities relevant to this mission in addition to the conduct of specific international programs of its own.

The international activities of the NIH serve many scientific purposes, dictated by the specific objectives of the intramural and extramural programs of the categorical Institutes and the support and service Divisions. Implementation of these activities must in turn be responsive to and consistent with national and international policies. FIC coordinative functions link the NIH with other components of the Department of Health and Human Services, the Department of State, the Immigration and Naturalization

Service of the Department of Justice, the U.S. Information Agency, foreign embassies in this country, science attaches, and multilateral organizations such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO). At the same time, international activities from year to year reflect changes in the health scene as advances are made and new challenges emerge. The NIH also recognizes the important needs of developing nations and has fostered contacts that are described in this report.

In its coordinative functions, the FIC has relied upon the cooperation of the BID's in providing the information for this report. Together we hope that the material is selected and presented in a way that is useful to a wide audience--including officials and the scientific community here and abroad--and illustrates the many ways international programs and activities contribute to biomedical and behavioral research and national health not only for the United States but also for the world at large. In assembling the overall report, we have made certain editorial modifications to the reports submitted by the individual BID's to achieve a consistent format. Because of size limitations, some deletions have been necessary. However, care has been taken not to alter the scientific content.

The first chapter of the report presents highlights of international activities that are described in greater detail in the individual BID chapters. In Chapter II, "Highlights of Recent Scientific Advances," we have chosen to emphasize two types of international research activities: international biomedical collaboration (between U.S. and foreign scientists) and research in which foreign locations or population groups are important to the furtherance of scientific knowledge. Chapter III, prepared by the Office of the Director, FIC, describes activities and accomplishments of the programs conducted by the Center, as well as its coordinative and administrative functions. Subsequent chapters discuss international programs and accomplishments of the individual BID's. Tables and figures summarizing NIH international activities in FY 1982 are appended.

In contrast to the previous report, there is no separate chapter on activities with individual

countries. Rather, we have provided two indexes: one that refers to descriptions of activities with individual countries and one that permits location of material on specific diseases, conditions, and research areas.

Within the limitations of a single report it is difficult to summarize the complex nature of NIH international activities and their contributions to betterment of health in the United States and abroad. Nevertheless, in this document we have attempted to provide information

of interest and use to a variety of audiences, and we welcome comments that will enable us to achieve more fully this objective for future reports.

Mark S. Beaubien, M.D.  
Acting Director  
Fogarty International Center and  
Acting Associate Director for  
International Research  
National Institutes of Health

# Contents

	page
Foreword . . . . .	iii
I Overview of International Activities . . . . .	1
II Highlights of Recent Scientific Advances . . . . .	3
Components of the National Institutes of Health . . . . .	9
III John E. Fogarty International Center for Advanced Study in the Health Sciences . . . . .	11
IV National Cancer Institute . . . . .	28
V National Heart, Lung, and Blood Institute . . . . .	45
VI National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases . . . . .	61
VII National Library of Medicine . . . . .	66
VIII National Institute on Aging . . . . .	70
IX National Institute of Allergy and Infectious Diseases . . . . .	73
X National Institute of Child Health and Human Development . . . . .	87
XI National Institute of Dental Research . . . . .	90
XII National Institute of Environmental Health Sciences . . . . .	93
XIII National Eye Institute . . . . .	99
XIV National Institute of General Medical Sciences . . . . .	103
XV National Institute of Neurological and Communicative Disorders and Stroke . . . . .	104
XVI Warren G. Magnuson Clinical Center . . . . .	107
XVII Division of Computer Research and Technology . . . . .	108
XVIII Division of Research Resources . . . . .	110
XIX Division of Research Services . . . . .	112
Appendix . . . . .	115
Index by Country . . . . .	128
Index by Research Area . . . . .	129

## Tables and Figures

Table	page
3-1. Scholars-in-Residence, 1982 . . . . .	14
4-5. Countries/areas of origin of ICRET awardees and their destinations, 1976-82 . . . . .	35
4-2. The exchange of scientists under NCI's bilateral agreements programs . . . . .	36
4-3. Patient data, by cancer site and collaborating institute, entered into the ICPDES system . . . . .	38
4-4. International cancer research technology transfer . . . . .	40
4-5. Countries/areas of origin of ICRET awardees and their destinations, 1976-82 . . . . .	41
4-6. The NCI-PAHO collaborative cancer treatment research program by number of protocols and patient accrual . . . . .	42
4-7. NCI-PAHO collaborative cancer treatment research program by location and number of active protocols . . . . .	44
7-1. National Library of Medicine non-U.S. MEDLARS Centers . . . . .	67
A-1. Total expenditures for NIH international programs, by activity and BID, FY 1982 . . . . .	120
A-2. NIH international research and research training awards by country/area and mechanism, FY 1982 . . . . .	122
A-3. NIH international research and research training awards, FY 1947-82 . . . . .	126

### Figure

1. NIH Organization Chart . . . . .	10
A-1. NIH international activities, funding by mechanism, FY 1982 . . . . .	117
A-2. NIH international research and research training awards, FY 1973-82 . . . . .	118
A-3. NIH international research and research training awards, FY 1973-82 . . . . .	119



# Chapter I

## Overview of International Activities

International activities relevant to the missions of the Bureaus, Institutes, and Divisions (BID's) are described in their separate chapters. This chapter highlights features of these activities that overarch the special roles of the NIH components, those that involve other agencies in the Public Health Service (PHS), other executive departments (e.g., Department of State), and such multilateral organizations as the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

The breadth and complexity of NIH international activities are clearly illustrated in the sections on bilateral agreements in the BID chapters of this report and especially in the section containing the report of the Fogarty International Center (FIC) that describes its international coordination and liaison activities. These agreements, which are links between foreign and U.S. Governments, are usually established through the Department of State. The biomedical programs may be part of broad science and technology agreements or of more specific health agreements. As of 1982, the NIH was participating in over 39 bilateral agreements involving 29 countries, the most recent additions being Kuwait and Nigeria (1981) and Finland (1982). Because numerous Institutes (in some instances as many as 9 or 10) and other PHS components participate in agreements with a given country, the liaison function of the FIC contributes to smooth coordination of complex relationships. The FIC may also initiate relationships with countries (coordinated with the State Department) and may involve appropriate BID's, depending on the nature of the scientific or disease area involved. The bilateral agreements have been of great value in reducing social and political barriers to scientific exchanges, in capitalizing on unique features of local environments and resources, and in fostering collaborative undertakings with shared technical and professional resources and shared costs.

Another source of funds for collaborative efforts is the Special Foreign Currency (P.L. 480) Program. As discussed in more detail in the report on the FIC International Research and Awards Programs, this source of support is being replaced, in most cases, by matching funds. These funds are administered by joint boards

established by the United States and the foreign country. The joint boards review and monitor individual projects of mutual interest.

All categorical components of the NIH, as well as the FIC, work closely with multilateral organizations, especially the WHO. The FIC coordinates NIH advice for the Department of Health and Human Services (DHHS) and its representation to the WHO concerning agenda, budget, and policy issues.

During FY 1982, the FIC was designated as the first WHO Collaborating Center for Research and Training in Biomedicine. This designation, which is for a 4-year period, provides a new kind of opportunity for the United States (via the NIH) to expand its leadership role in international biomedical sciences. Activities in the planning stage include expanded information exchange and strengthened linkages with counterpart research organizations in other countries.

An objective measure of other NIH cooperation with WHO is the number of other BID's that serve as WHO Collaborating Centers:

- The National Cancer Institute (NCI) is a Collaborating Center for Reference on Tumors of Laboratory Animals.
- The National Heart, Lung, and Blood Institute (NHLBI) is a Collaborating Center for Research and Training in Cardiovascular Diseases for the Americas.
- The National Institute on Aging (NIA) is a Collaborating Center for Joint Cooperation on Research on Care of the Aged.
- The National Institute of Allergy and Infectious Diseases (NIAID) is a Collaborating Center for Rickettsial Reference and Research, Mycoplasma Reference and Research, Virus Reference and Research, and Interferon.
- The National Institute of Dental Research (NIDR) is a Collaborating Center for Research in the Prevention of Dental Caries and Periodontal Diseases.
- The National Institute of Environmental

Health Sciences (NIEHS) is a Collaborating Center for Environmental Health Effects.

- The National Eye Institute (NEI) is a Collaborating Center for the Prevention of Blindness.
- The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is a Collaborating Center for Research and Training in Neurosciences.
- The Division of Research Resources (DRR) is a Collaborating Center for Reference and Research in Simian Viruses.
- The Division of Research Services (DRS) is a Collaborating Center for Defined Laboratory Animals.

The intramural NIH scientists have been a valuable resource to the FIC, bringing their expertise to bear when serving as nominators and reviewers of Scholars-in-Residence, as members of the Scholars-in-Residence Advisory Panel, or as members of the FIC secondary review group for Senior International Fellowships, International Research Fellowships, or International Conference Awards. In turn, the FIC contributes to the intramural programs of the NIH Institutes through its Foreign Scientists Assistance Programs, which provide coordination, guidance, and assistance to the BID scientific directors and to the foreign scientists who are invited to the NIH as Visiting Fellows, Visiting Associates, Visiting Scientists, or Guest Researchers. In FY 1982 this activity involved over 1,400 scientists from over 60 countries.

Through the International Issues Study-Program, the FIC also involves appropriate BID scientists in studies by special task forces of selected topics of international relevance.

More specific accomplishments under each of these programs are described in the chapter on the programs of the FIC.

The scientific community at the NIH and that supported by the NIH through its extramural programs have extensive relationships with over 60 countries worldwide. Selected scientific highlights of these activities are reported in the next chapter.

Tabular and graphic summaries of NIH international activities are presented in the appendix. In FY 1982, \$62 million of NIH's total appropriation of \$3.6 billion was devoted to international activities (see table 1, Appendix). This constitutes about 1.6 percent of the NIH appropriation. This proportion has remained stable in recent years. Of this \$62 million, about \$21 million, or 34 percent, supported scientist exchanges: foreign scientists conducting collaborative research in the United States and U.S. scientists conducting research abroad (\$15.7 million of this

amount was devoted to the support of foreign visiting scientists who conduct collaborative research with intramural scientists at the NIH). Another \$11.4 million, or 22 percent of the amount spent on NIH international activities in FY 1982, was devoted to support of research grants held by foreign investigators. These awards have been reviewed for scientific excellence, for BID program relevance and priority, and for assurance that performance in a foreign country would yield a particular value. About \$12 million, another 17 percent, was used to support foreign contracts that are awarded only after competitive peer review and justification for the conduct of the research in the foreign country. The remainder supported international conferences, travel, and bilateral and staff exchanges. Almost half of the \$62 million devoted to international programs was actually expended in the United States on activities including support for foreign scientists and Fogarty Scholars who study in the United States, travel, and bilateral exchanges to the United States of foreign scientists. Appendix figure 1 depicts these activities by broad categories of program mechanisms.

Appendix table 2 displays the FY 1982 expenditures for research and research training awards, by country or area and type of award. Most of the foreign grants and contracts were awarded to scientists in Canada -- \$7.4 million -- with scientists from Israel receiving awards in the amount of \$4.4 million; those from the United Kingdom, \$3.5 million; and those from Japan, \$3.4 million. Australia, Brazil, Egypt, India, Italy, and Sweden were awarded totals of \$1 million to \$3 million.

International organizations including WHO, PAHO, and the International Agency for Research on Cancer (IARC) were awarded about \$3.7 million in grants or contracts in FY 1982.

Appendix table 3 provides information on trends of NIH international research and research training awards. These activities reached a level of \$49 million in FY 1982. These amounts include the \$1.4 million in awards made from Special Foreign Currency (P.L. 480) money. This money is appropriated to the Office of the Assistant Secretary for Health, DHHS, and is reviewed and administered by the NIH.

Over the past 10 years, Visiting Program support and research grants to foreign scientists have increased to a greater extent than have other types of international activities. The amount devoted to international research contracts remains at about \$11 million. These trends are depicted in figure 2 in the appendix. In terms of constant 1973 dollars, however, the amount devoted to international research and research training awards in FY 1982 was only slightly more (\$23 million) than the FY 1973 amount of \$19.6 million. These trends are depicted in figure 3 in the appendix.



## Chapter II

### Highlights of Recent Scientific Advances

The following highlights present a selective summary of scientific activities and accomplishments under international research programs sponsored by the Bureaus, Institutes, and Divisions of the NIH. Drawing upon detailed reports submitted by the BID's, this chapter places the activities and accomplishments in the context of global health problems and illustrates the benefits of international collaboration in biomedical research. Some studies between the United States and other countries are reported here because they employ innovative research approaches or new technologies or examine special populations, even though the projects are in the early stages. They are relevant because they are opening new paths to the solution of health problems of international concern.

Two types of projects have been selected for special reporting here: first, collaborative biomedical projects in which scientists from the United States and at least one other country participate to develop new knowledge that will lead to the prevention or alleviation of diseases or afflictive conditions; and second, epidemiological studies, in which scientists, working collaboratively, take advantage of the availability of specific cultural settings and environments in various parts of the world. These groups have often been valuable resources for the study of disease prevention and disease control using epidemiologic methods of investigation. Through their international research programs, the Institutes of NIH have engaged in cooperative epidemiologic studies with foreign countries when particular features were eminently suitable for learning about factors that cause or influence the course of a disease. In some instances, a population has been exposed to environmental factors rarely found elsewhere, or a group with a common genetic background provides enough individuals with a genetically determined disease to be suitable for an epidemiologic study. In still other instances, studies drawing on an ethnic background make it possible to trace the influence of such factors as dietary habits, behavior patterns, and lifestyles on the incidence and prevalence of a disease.

Recent accomplishments and ongoing projects of these two types of activities are described below.

#### International Collaborative Projects to Prevent or Alleviate Disease

Collaborative research between NCI scientists and those of China on the biochemical epidemiology of cancer of the esophagus has revealed that in Linxian Province staple food is heavily contaminated by a *Fusarium* genus. They have found that T<sub>2</sub> toxin produced by *Fusarium* has both direct cytotoxic and proliferative effects on fetal esophageal epithelium. At high dosage of the toxin, cultured epithelial cells became necrotic, whereas at lower doses the toxin caused mitogenic effects including focal basal cell hyperplasia, dysplasia, and increased numbers of mitoses. Atypical mitoses were also observed. These changes are very similar to the premalignant lesions seen in epithelium adjacent to human esophageal carcinoma. The lead established in China on the possible role of a fungal mycotoxin in human esophageal carcinogenesis is being pursued in a quantitative way.

By virtue of the agreement between the NCI and the Japanese Society for the Promotion of Science, teams of American and Japanese virologists independently isolated and identified retroviruses that are associated with a human T cell leukemia virus (HTLV) and the adult T cell leukemia virus (ATLV), respectively. These are newly identified human retroviruses, which seem to be identical or very similar to each other. The viruses are closely associated with mycosis fungoides, Sezary syndrome, and adult T cell leukemia, which belong to the category of differentiated T cell lymphoma and leukemia. The viruses have been found to be endemic in the southwestern part of Japan and certain Caribbean Islands.

During his sojourn in the Institute of Oncology in Warsaw, Poland, an American pharmaceutical chemist collaborated with Polish counterparts on the synthesis and quality-control testing of P-32 labeled ion exchange resin microspheres for radiation therapy of hepatic neoplasms. Representative samples of the microspheres were injected intraperitoneally into rats. Because of the low uptake of the radioactive microspheres by the liver following intraperitoneal injection, a

new approach was adapted for administration of the microspheres. Increased absorption of the radioactive agent occurred after delivery via a catheter inserted into the hepatic artery. Information gained from trials in experimental animals is expected to show that a larger number of the smaller microspheres will deliver a radiation dose more exactly matching the distribution of capillary blood flow. It is believed that the radiation therapy from the beta decay of P-32 microspheres, when combined with surgery and/or chemotherapy, will result in a better and longer life for the cancer patient.

A visiting Hungarian scientist, working with his American counterpart at the Roswell Park Memorial Institute, studied methods of tumor cell disaggregation--mechanical and enzymic--for yielding single cell suspensions. Among 17 tumors studied, the number of cells obtained by disaggregation differed widely. Considering the disaggregated samples as the starting material, researchers found the recovery rate ranged from 30.7 to 82 percent, with a mean value of 49 percent and 56.3 percent, respectively, for mechanically and enzymically disaggregated samples. A high degree of separation of tumor cells from leukocytes and red blood cells occurred, the separation of macrophages from tumor cells being more difficult. Intracellular concentration of the anticancer agent Ara-C and <sup>3</sup>H-thymidine was higher in the fractions with more viable cells. The effect of another anticancer agent, DDP, was opposite in that the results suggest an intensive binding to nonviable cells. Thus, it seems important to separate more clearly the viable and nonviable cells to determine whether the reduced or increased uptake of precursor or drug in nonviable cells is due to metabolic failure or whether the nonviable cells represent a metabolically distinct population with preserved growth potential.

Ten American cancer centers and 13 cancer institutes in Latin America are participating in the Collaborative Cancer Treatment Research Program (CCTRP) established between the NCI and PAHO, where 26 active cancer treatment protocols are now being investigated. Over the total life of the program as many as 37 protocols have been active in a single year. Eleven protocols have been completed or terminated.

During the 4 years that this program has been in full operation, 2,342 patients have been accrued in the various protocols. An effective international collaborative research program, the CCTRP shows itself an excellent medium for (1) promoting and practicing, at the international level, the concept that clinical research is the best means to prove the effectiveness of a given treatment; (2) identifying the most satisfactory techniques for a given trial and promoting their standardized use; (3) accelerating results by pooling efforts and resources; (4) stimulating the design of innovative studies attempt-

ing to solve questions of local as well as of international interest; and (5) opening channels of communication for the exchange of new ideas and the comparison of results from institutional and individual accomplishments.

As a result of exchanges between American hosts and two visiting Soviet chemotherapists, a protocol was drafted for a Phase I Clinical and Pharmacologic Trial of Platinumdiammine (CBDCA). The joint study is underway as a collaborative effort between the University of Maryland Cancer Center and the All-Union Oncologic Scientific Center in Moscow. Paralleling the studies being pursued in the United States, the Soviet effort includes (1) establishing the maximum tolerable dose of CBDCA in cancer patients; (2) evaluating CBDCA toxicity in patients with previously treated and untreated malignancies; (3) determining the antitumor activity of CBDCA; and (4) determining the clinical pharmacokinetics of the anticancer agent.

Significant progress has been made in the collaborative studies of the biochemical epidemiology of human esophageal and liver cancers by American and Chinese scientists. Methods to culture human esophageal and liver tissues have been established in China. From experimental studies, it has been determined that these tissues, in culture, retain the capacity to activate aflatoxin B<sub>1</sub>, benzo(a)pyrene, and N-nitrosodimethylamine. These and other carcinogen-DNA adducts have been identified by high-pressure liquid chromatography. Progress is being made as well in establishing the conditions to culture monolayers of human hepatic and esophageal epithelial cells.

Collaborative research has been conducted with personnel of the Cairo Cancer Institute through a formal bilateral agreement with Egypt. Recently, a Phase II study of chemotherapeutic agents, initiated in 1976, was completed. Twelve drugs were studied in about 400 patients with squamous and transitional cell bilharzial bladder carcinoma. The drugs included hexamethylmelamine, VM26, methotrexate, bleomycin, adriamycin, platinum, cytoxan, 5-fluorouracil, trenimone, m-AMSA, vincristine, and pentamethylmelamine. Notable response rates were seen with hexamethylmelamine, pentamethylmelamine, vincristine, and trenimone. On the basis of these results, an active chemotherapy combination might include vincristine, pentamethylmelamine, and 5-fluorouracil. The durable response rate after radical cystectomy in bilharzial bladder carcinoma is 35 percent (5-year disease-free survival), which is not improved by pre- or postoperative radiotherapy. Thus, initiation of a controlled trial of radical cystectomy plus or minus adjuvant chemotherapy is timely. The combination described is under active consideration, as are other combinations.

During the course of U. S. - U. S. S. R. collaboration under the bilateral agreement in the



cardiovascular area, scientific progress has been made on a number of topics. This year the targeting of drugs to injured heart muscle has received special attention.

Soviet scientists have developed synthetic liposomes, a microscopic colloidal fat particle, suitable for injection. In recent years, researchers have recognized liposomes as promising carriers for drug transport in vivo. However, the relatively rapid clearance of the liposomes, which results from their capture by cells of the reticuloendothelial system primarily in the liver, still limited their everyday clinical use. A Soviet investigator working with a U.S. colleague has now succeeded in linking antibodies specific for cardiac myosin to liposomes. When cardiac muscle is damaged by lack of oxygen, unique intracellular antigens are uncovered, which are recognized by this liposome-antibody complex. An antibody-antigen interaction occurs that binds the liposomes to the damaged cardiac muscle. By adding an isotopic marker to the drug liposome complex, scientists can visualize the damaged muscle simultaneously as the therapeutic agent is rapidly and preferentially applied to it. The binding of the liposomes to the cardiac muscle also slows their excretion, thereby prolonging the efficacy of action of the drug that they are transporting.

Sickle cell anemia is a hereditary disease that affects 50,000 black Americans and perhaps 2 million people worldwide, mostly in Africa. This condition results from an abnormal hemoglobin, called hemoglobin S, which polymerizes or aggregates upon deoxygenation and distorts the blood's red cells into an elongated, sickle-like shape. Recent research indicates that the inflexibility inherent in such "sickled" cells (not the shape per se) leads to the tissue damage and destruction of red blood cells that is characteristic of this severe, and even fatal, disease.

Intramural scientists at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) have conducted extensive investigations into the polymerization process that characterizes hemoglobin cells in sickle cell anemia.

In the search for a therapy for this disease, recent collaboration between investigators in NIADDK's Laboratory of Chemical Biology and foreign investigators has been particularly helpful. For instance, a Fogarty Scholar-in-Residence from Japan has provided singular ingenuity in suggesting the synthesis of individual peptides that might block the gelation (polymerization) of hemoglobins. In another instance, collaboration with a British scientist may lead to discovery of the mechanism whereby certain peptides can inhibit the gelation of hemoglobin.

This research could ultimately result in a rational and effective therapy for sickle cell anemia, both in the United States and in Africa, and could provide an outstanding example of the

cross-fertilization that often evolves from international scientific collaboration.

## International Collaborative Projects to Study Disease Etiology and Identify

### Risk Factors

Increasingly, investigators are convinced that to prevent or minimize the adverse effects of environmental factors, adequate methodologies to predict the toxicity of these environmental factors must be developed. NIEHS scientists, through multilateral and bilateral agreements in collaboration with scientists throughout the world, have played a leading role in assessing current methods and developing better methodologies for assessing the toxic potential of environmental chemicals. Major emphasis has been placed on international collaboration aimed at developing better short-term methods for detecting whether chemicals can cause such toxic effects as genetic mutations, birth defects, and damage to various organ systems. For example, recent remarkable advances in the fields of genetics and mutagenesis have revolutionized the fields of toxicology and carcinogenesis by providing new short-term test methods to reveal whether chemical substances can damage DNA. Detection of damage to DNA has important implications for carcinogenesis and heritable genetic diseases. Clearly, a number of factors interact to determine the ultimate action of chemical mutagens and carcinogens. Under the U.S.-Japan Cooperative Medical Sciences Program, Japanese and American scientists have successfully identified dietary factors capable of enhancing or inhibiting the mutagenic activity of substances found in food. For example, mutagenic and carcinogenic compounds from broiled fish and ground beef have been isolated and identified. Additional tests are being conducted with a variety of other foods that can reduce the activity of the mutagens in cooked meats. These studies may eventually lead to the prevention of cancer and genetic diseases in which diet is a contributing factor.

Exposure to physical environmental factors has also become of growing concern as the number of emission sources has increased. Under the U.S.-U.S.S.R. Medical Science and Public Health Agreement, joint studies on the biological effects of microwave radiation, and static and low frequency electromagnetic fields are underway. Now that a detailed protocol for a duplicate experiment has been developed, both sides will compare the same behavioral, electrophysiological, and biochemical methods under exposure conditions as identical as possible. The purpose is to determine, first, whether both groups will



observe the same effects and, second, which methods appear to be the most sensitive. It is hoped that this study will provide insights into the reasons why Soviet scientists generally report effects of electromagnetic waves on the nervous system at exposure levels below those reported in the United States.

The impact of migration on cardiovascular disease is an important public health concern. After studying variations in motivations and personal characteristics of migrants and nonmigrants, scientists have discovered significant differences in disease patterns. Filipino migrants, for instance, experience higher risk of hypertension and death due to cardiovascular disease after migration to Hawaii or California. Similar increases were reported for Japanese migrants to these areas. Although hypertension is a major health problem in both Asians and Europeans, in Asians the most prevalent sequela is stroke, while in Europeans heart attack is the most frequent outcome. The changing risk experienced by Asian migrants to westernized areas indicates a large environmental factor in the etiology of cardiovascular disease. Yet, the process of westernization has resulted in conflicting patterns of cardiovascular disease in different countries. In the Philippines this process, which includes a Western diet, is accompanied by an increased risk of coronary heart disease, while in Japan coronary heart disease is decreasing in spite of westernization and increased consumption of saturated fats. Examination of these differences may uncover clues to the relative importance of the various known risk factors in the etiology of cardiovascular disease. More important, it may lead to further decrease in cardiovascular disease through a lessening or elimination of these risk factors.

An extremely high incidence of Huntington's disease (HD) exists among certain residents around Lake Maracaibo in Venezuela, all reportedly descended from a Spanish sailor who arrived in the country in 1860. Scientists at the University of Zulia in Maracaibo are working with NINCDS scientists and grantees on a study of over 200 HD patients in the area and 2,000 of their relatives.

Since these Venezuelans have all inherited an identical HD gene, they are particularly valuable subjects for research. In addition, several families have intermarried, creating the possibility that some descendants may carry two genes for HD. These features make this community unique in the world. No one knows whether such a "double dose" of the gene would be lethal to the fetus or would greatly shorten the life of any child born alive; however, if individuals carrying two genes for HD can be found, they would be ideal subjects for studying the precise metabolic abnormality arising from the defective gene.

In 1981 and 1982, the NINCDS conducted two scientific expeditions in Venezuela. Venezuelan

HD patients and at-risk family members were examined neurologically and psychologically, were filmed to document clinical status, and were administered medical history questionnaires. Blood and skin samples have been taken from over 260 patients, family members, and controls and have been sent to NINCDS grantees for analysis. The Venezuelan pedigrees collected so far have been computerized and are now part of an NINCDS-supported Huntington's Disease Research Roster at the University of Indiana.

Grantees using the Venezuelan cell lines are generating "maps" identifying the location of the patients' genes on the chromosomes. These maps will be useful for locating any defective gene causing inherited disease, as well as for understanding normal inheritance. This research, on the forefront of neurogenetic investigations, holds tremendous promise, not only for controlling Huntington's disease, but also for alleviating suffering worldwide.

In FY 1982, the NINCDS continued to expand its program in neuroepidemiology, a major portion of which entails collaboration with scientists and health workers in other countries.

The failure of governments and health agencies in most developing countries to measure accurately the extent of various disorders creates a serious problem. Many have few resources for such measurement and no usable data. To begin to meet this need, the NINCDS and WHO have developed a screening examination and questionnaire that can be used by lay health workers and have joined with health officials to pilot test the examination and questionnaire in Nigeria, Mexico, and China. The examination and questionnaire are designed specifically to find cases of cerebrovascular disease, epilepsy, extrapyramidal disorders, brain tumors, peripheral neuropathies, and migraine headache. They are also designed to facilitate statistical comparisons among countries. Two interesting preliminary findings have come from the early data: rural Nigerian populations have a prevalence of migraine headaches similar to residents of major U.S. and European cities; and China has the highest prevalence of cerebrovascular disease of any country in the world where the problem has been studied. The NINCDS, WHO, and officials in China, Nigeria, and Mexico are now planning the project's second phase, which will study possible risk factors. A third and final phase should determine the best methods of control and prevention.

A number of other countries—including Peru, Colombia, Venezuela, Kenya, India, and Senegal—are adapting the questionnaire and examination for their own purposes.

The NIA, still in the first decade of development, continues to participate in activities that promote general scientific cooperation among national institutes and programs of gerontology around the world. Outstanding research projects



of high scientific merit that are particularly relevant to NIA programs are in some cases more directly supported by the Institute.

One such example is a collaborative project the Institute has developed with a French expert on studies relating to dihydroepiandrosterone (DHEA). Worldwide interest in this naturally occurring hormone is increasing, because the DHEA level decreases with age and abnormal levels are observed in many pathological states. Research results and theoretical interpretations of these results vary considerably and tend to be quite controversial.

Because it is important to understand the relationship of this hormone to the aging process, the NIA Biomedical Research and Clinical Medicine Program has entered into a cooperative arrangement with a well-known investigator from the University of Paris to examine naturally occurring levels of DHEA in the tissues of mice and rats supplied from NIA colonies of aged animals. These analyses are expected to yield important information to the NIA on the value of mice and rats as models for DHEA research and at the same time contribute to the investigator's DHEA research program in France.

The populations in the Pacific region and the health impact of their migration to the United States offer a wide range of opportunities to extend our knowledge of how environmental and genetic factors interact to influence cardiovascular disease patterns. In order to explore and evaluate these scientific opportunities, the NHLBI held an international workshop on the Changing Patterns in Cardiovascular Disease in the Pacific Basin, in January 1982. Data were presented from the following countries and regions: China, Taiwan, the Philippines, Australia, New Zealand, Micronesia, Hawaii, other islands of the South Pacific, and the WHO Region for the Western Pacific. The scientists recommended that these unique opportunities for specialized studies in the Pacific region be exploited to the utmost. To take advantage of already available baseline information and disease prevalence data, investigators must complete incidence followup examinations in the Guam and Palau survey populations and the California cohort of the NI-HON-SAN Study (Japanese living in Japan, Hawaii, and California). Standardized surveillance of cardiovascular disease trends and risk factors needs to continue in Fiji, the Philippine Islands, and several Pacific Island groups where cardiovascular disease and associated risk factors appear to be increasing. New insights into the relative roles of the environment and genetics in the etiology of cardiovascular disease may result from studies of the causes of urban-rural differences in the Philippines and Fiji and of serum cholesterol levels in Japan, the North-South differences in hypertension prevalence in China and Japan, the different coronary heart disease mortality rates among migrants and

nonmigrants in Australia, and the different risk of cardiovascular disease among Indians and Fijians in Fiji.

Because sudden infant death syndrome occurs primarily during sleep, a better understanding is needed of the effects of development on sleep cycles and of the interaction between the sleep cycle and respiratory activity. Studies underway in Australia using immature and adult marsupials, called potoroos, will help to determine developmental characteristics of respiratory control during sleep. Because marsupial offspring are born at a very early stage of development and continue developing in the marsupial pouch, this particular animal offers the unique advantage of easy access to young mammals at stages corresponding to the fetal or intrauterine periods in other species.

In the Dominican Republic, investigators supported by the National Institute of Child Health and Human Development (NICHD) have been working with a pediatrician to study an unusual group of Dominican children who are born genetically male, but because of a congenital enzyme deficiency (5-alpha-reductase), their external genitals appear to be female.

At the time of puberty, these children who have been raised as girls suddenly act like boys: a dramatic switch of gender role occurs even without phallic development. This complete sexual reversal clearly demonstrates that gender identity is not fixed in early childhood and that testosterone profoundly affects the brain at the time of puberty in establishing male identity and behavior patterns. These discoveries have important implications for the therapy of children who are born with other kinds of sexually ambiguous genitalia.

In Asia a cross-cultural study of the factors that determine the timing of first births has revealed the apparent universality of the effects of socioeconomic variables, such as education or rural/urban origins, on the timing. In Asian societies as dissimilar as Hong Kong and the Philippines, these variables have the same effect; yet the importance of cultural heritage remains.

After other factors are taken into account, the Confucian heritage groups have substantially later ages at first birth than the Muslim and Hindu groups, with substantially younger ages at first birth. The study also has shown that increases in age at marriage found in many developing countries have not had so great an impact on reducing fertility as once thought. In general, the later the age at marriage, the sooner the first birth occurs and the higher the level of early marital fertility.

Two researchers from Brock University in Canada have collaborated with the Physical Sciences Laboratory of the DCRT in studying the theory and measurement of intermolecular forces. This project has succeeded, for the first

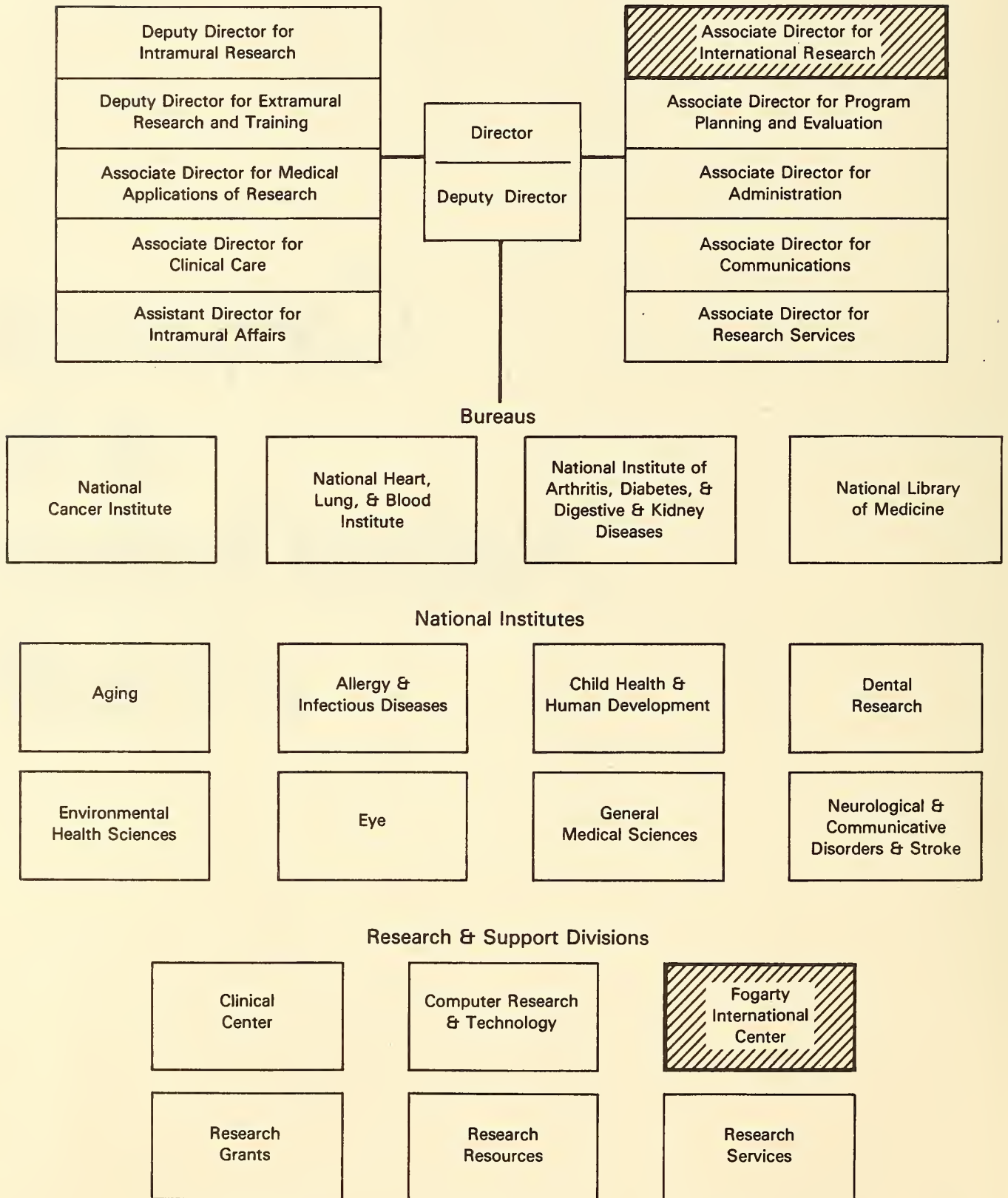
time, in directly measuring the force between biological macromolecules, providing a good picture of how the force between parallel DNA helices behaves in response to changes in

distance, as well as elucidating the effect of structure on this force. An extension of the work will allow the determination of important thermodynamic parameters of proteins.

*Components  
of the  
National Institutes  
of Health*

Figure 1.--NIH organization chart

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH**





# Chapter III

## John E. Fogarty International Center for Advanced Study in the Health Sciences

### Introduction

The Fogarty International Center for Advanced Study in the Health Sciences (FIC) was created in 1968 to provide a focus and organizational mechanism for NIH activities in international biomedical research. The mission and objectives of the FIC are to:

- Facilitate the assembly of scientists and leaders in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of science internationally as it pertains to health and its implications and applications for the future;
- Further international cooperation and collaboration in the life sciences through its research programs, conferences, and seminars;
- Provide postdoctorate fellowships for training in the United States and abroad and promote senior scientist exchanges between the United States and other countries;
- Coordinate NIH activities and functions generally concerned with health sciences at an international level; and
- Serve as a focal point for foreign visitors to the National Institutes of Health.

The Director, FIC, is also the NIH Associate Director for International Research, in which capacity he advises the Director of the NIH on the development of international policies and procedures related to health. On international issues the FIC interacts with each of the BID's of the NIH, as well as with other components of the Department of Health and Human Services. In addition, the FIC maintains liaison with the Department of State and other Government agencies, with foreign embassies, and with multinational and foreign organizations.

The FIC discharges its responsibilities through four program activities: Advanced International

Studies, Foreign Scientists Assistance, International Research and Awards, and International Coordination and Liaison. The FIC also provides core support for the Gorgas Memorial Laboratory in Panama.

During FY 1982, the FIC was designated as the first WHO Collaborating Center for Research and Training in Biomedicine for a 4-year period. The FIC has begun to fulfill its role as a WHO Collaborating Center by expanding its information exchange activities and linkages with counterpart research organizations in other countries.

Additional FIC program highlights during FY 1982 were the initiation of a Nominating Committee for the International Research Fellowship (IRF) Program in China, the reactivation of the IRF Nominating Committee in the West Indies, and the negotiation of an agreement between the FIC and the Alexander von Humboldt Foundation in the Federal Republic of Germany for the FIC to announce the availability of German fellowships for U.S. scientists.

Specific program activities and accomplishments are presented in the following sections.

### Advanced International Studies

The goal of Advanced International Studies Programs is to facilitate international scientific communications by providing international forums for the exchange of scientific information and for the review and evaluation of major areas of biomedical research, particularly as related to international health problems of mission interest to the National Institutes of Health.

Advanced international studies in the health sciences are aided through three FIC inter-related programs: International Issues Study-Program, International Conferences and Seminars Program, and Scholars-in-Residence Program. The fundamental purpose of these programs is to review and evaluate recent research results and the derivative knowledge so that the best directions for further scientific research to overcome or avoid major health problems will be apparent. These activities tap scientific talent, not only throughout the United States, but also

in any country in the world where it exists. The major goal of these programs is to evaluate and transfer new knowledge and technologies to organizations and individuals to whom the new information will be useful.

### **International Issues Study-Program**

This program effort is devoted to harnessing the best pertinent health science talent in the world to analyze major health problems of multicountry interest and to give advice and guidance to national health authorities on actions to be taken, individually and collectively, to overcome the problems. Issues addressed include international aspects of biomedical and behavioral research, research manpower training, and the transfer of research results to bring new knowledge to bear where it will benefit health worldwide.

Identification of aspects of the problem calling for further research is of paramount interest in each project. Some projects are described below.

#### **International Conference on the Eradication of Infectious Diseases**

Published in the Sept.-Oct. 1982 (Vol. 4, No. 5) issue of Reviews of Infectious Diseases were the proceedings of the International Conference on the Eradication of Infectious Diseases, conducted by the FIC and a number of other agencies in May 1980. At that conference the participants analyzed the nature of the program activities that led to the world eradication of smallpox. With those procedures in mind, they then determined their applicability to other infectious diseases. Among the recommendations stemming from that evaluation were separate, in-depth analyses of measles, poliomyelitis, and yaws. The FIC has moved to accomplish these analyses, each with the relevant national and international health-related agencies.

#### **International Symposium on Measles Immunization**

Conducted in March 1982, this international symposium accommodated the enthusiastic participation of scientists from many parts of the world. During the assessment of the current impact of measles on the world population, participants gave particular attention to comparing countries with and without special vaccination programs, discussed strategies for the attainment of a high level of immunization, and evaluated prospects for eventual eradication. They identified aspects of the disease and of its control that need further research. The participants concluded that the challenge is to exploit the

available vaccines and to overcome the remaining economic, logistic, and attitudinal barriers. Participants returned home resolved to eliminate measles as a universal cause of childhood misery and of long-term disabilities. Proceedings of the symposium were submitted for publication in Reviews of Infectious Diseases.

#### **International Symposium on Poliomyelitis Control**

Extensive plans were made for this project, which is scheduled for March 14-17, 1983, in the Headquarters Building of the Pan American Health Organization. The focus of the symposium will be on control of poliomyelitis by means of immunization. Applicable to future programs to advance such control in both developed and developing countries, these recommendations will be based on assessment of up-to-date knowledge concerning the viruses themselves, the current status of poliomyelitis in various parts of the world, and the vaccines now available. Consideration will be given to political, economic, and administrative aspects as they impede or facilitate immunization strategies and to the feasibility of elimination of paralytic poliomyelitis in the foreseeable future. Emphasis will also be on identification of research needs and on new developments and their potential contribution to improved vaccines. This project is being jointly sponsored by the FIC, NIAID, NICHD, and NINCDS of the NIH; Centers for Disease Control, PHS; National Center for Drugs and Biologics, Food and Drug Administration (FDA); U.S. Agency for International Development; Institute of Medicine, U.S. National Academy of Sciences; WHO; PAHO; American Public Health Association; Infectious Diseases Society of America; National Foundation for Infectious Diseases; The Rockefeller Foundation; Merieux Institute, Inc.; Smith KlineRIT; Lederle Laboratories; and Hoechst Aktiengesellschaft.

#### **International Symposium on Yaws Control**

Planning occurred during 1982 for this symposium, which is scheduled for November or December 1983. It will involve scientists from all the tropical and subtropical areas of the world and, in total, the discussions will cover all three endemic treponematoses: yaws, pinta, and endemic syphilis. The main purpose of the symposium will be to assess the current impact of yaws and of yaws control efforts in the world; to review current technology and strategies relevant to control of yaws; and to consider the feasibility of yaws eradication. Aspects of this disease and its control that need further research will be identified. The proceedings of the symposium will be submitted for publication in a journal of broad readership, e.g., Reviews of Infectious Diseases.



## International Conferences and Seminars Program

The International Conferences and Seminars Program fosters advanced international studies in the health sciences through scientific meetings and conferences that provide opportunities for biomedical and behavioral scientists from various parts of the world to share their knowledge, ideas, and concerns about international health issues and to discuss current and future research endeavors and problems.

Good scientific communications are fundamental to a productive biomedical research program and to effective practical use of the results of biomedical research. Therefore, the FIC places a high priority on the planning and conduct, or funding support, of scientific symposia, conferences, and workshops. These FIC-supported meetings are of two types: intramural and grant supported. In FY 1982, the FIC provided partial or total funding support for 8 intramural conferences and partial funding support for 48 grant-supported conferences.

Intramural conferences are arranged by Fogarty Scholars as well as by NIH intramural scientists and FIC staff. The subjects of these meetings are of broad scientific interest and draw outstanding scientists from many parts of the world as participants. In FY 1982, the FIC supported one intramural conference, Catechol Estrogens, organized by the Director of the NIH Clinical Center. The remainder were organized by Fogarty Scholars alone or in conjunction with NIH intramural scientists. These conferences are described in the subsequent section on the Scholars-in-Residence Program.

Grant-supported conferences are initiated by non-NIH scientists who seek funding through grant applications. The NIH Division of Research Grants receives these applications, which are often given multi-Institute assignments according to their specific scientific nature. For those applications that are international in nature or have an international aspect, the FIC joins with the other assigned Institutes in the review of the applications and their funding, if approved. Examples of conferences supported by the FIC in FY 1982 follow.

### VI International Symposium on Atherosclerosis

The disease process that predisposes individuals to heart attacks and stroke is atherosclerosis (hardening of the arteries). Restriction of blood circulation due to atherosclerosis deprives the heart and other organs of necessary oxygen and nutrients. Vital arteries are narrowed by mounds or plaques on the inside wall in a process that may take years and is associated with a number of risk factors. The most important putative risks are excessive blood cholesterol in the form of elevated low-density lipoproteins, high blood pressure, and cigarette smoking.

Hardening of the arteries is the basic cause of coronary artery disease, the major cause of death in America. However, during the past decade there have been a 25 percent decrease in age-adjusted coronary heart disease and a 37 percent decrease in age-adjusted stroke mortality. This reduction is probably attributable to two factors: first, lifestyle changes reducing risk factors and, second, improvements in care of the patient in the acute phase just after a myocardial infarction.

The FIC and the NHLBI provided sponsorship and partial funding support for the VI International Symposium on Atherosclerosis, which convened in West Berlin in July 1982.

The general theme of the symposium, which attracted more than 1,500 scientists from many countries, was the causes and prevention of atherosclerosis and its complications. The prospect for preventive cardiology seems bright. The decline in heart disease in America and the associated clear evidence of changing lifestyles due to a decrease in the use of tobacco products, a reduction in the consumption of high saturated fat/high cholesterol foods, an awareness of the benefits of physical exercise, control of obesity and hypertension, all suggest an encouraging trend. However, heart disease remains a major problem.

The scientific program focused on the most basic aspects of the disease process. The proceedings of the symposium will be published, and it is expected that this volume will be a valuable source of information concerning progress in atherosclerosis research.

### Fifth International Symposium on Human Chlamydial Infections

Human chlamydial infections are transmitted from person to person by sexual contact. Serious health consequences result, affecting not only male and female partners, but also newborn infants. In the United States it is estimated that 25,000 cases of pneumonia and 50,000 eye infections in infants are caused yearly by Chlamydia.

Chlamydial infections are the most prevalent of the sexually transmitted pathogens. Pelvic inflammatory disease is the most serious complication from chlamydial and gonorrheal infections, causing sterility and ectopic pregnancies with possible fatal consequences to mothers. Pelvic inflammatory disease often causes damage to the female reproductive tract, resulting in about 50,000 major surgical procedures each year in the United States.

European scientists are at the forefront of the clinical and epidemiological research and control aspects of chlamydial infections. The FIC and the NIAID joined in providing partial funding

Table 3-1.--Scholars-in-Residence, 1982

Scholar's name and country	Discipline and home institution	Date of arrival	Date of departure
Shmuel Shaltiel, Israel	Biochemistry Weizmann Institute of Science	08/24/81	04/24/82
Tomas Hokfelt, Sweden	Neurobiology, Karolinska Institutet	09/01/81	06/15/82
Klaus Kuhn Federal Republic of Germany	Biochemistry Max Planck Institute for Biochemistry	10/01/81	09/30/82
Samuel Barondes, United States	Psychiatry, Univ. of California, San Diego	10/01/81	12/31/81
Franklin Bunn, United States	Hematology, Peter Bent Brigham Hospital	01/01/82	03/31/82
David Shemin, United States	Biochemistry, Northwestern University	01/01/82	04/01/82
Rolf Luft, Sweden	Endocrinology, Karolinska Institutet	02/01/82	04/30/82
Herman Kalckar, United States	Biochemistry, Boston Univ. Grad School	02/01/82	04/30/82
Irwin Gunsalus, United States	Biochemistry, University of Illinois	02/11/82	04/30/82
Helmut Holzer, Fed. Rep. of Germany	Biochemistry, University of Frieberg	02/15/82	05/15/82
Howard Schachman, United States	Biochemistry, Univ. California, Berkeley	04/01/82	06/30/82
Theodor Wieland, Fed. Rep. of Germany	Biochemistry, Max Planck Institute	04/01/82	06/26/82
M. Manago-Grunberg, France	Biochemistry Institut de Biologie Physico-Chimique	04/01/82	08/07/82
Bracha Ramot, Israel	Hematology The Chaim Sheba Medical Center	04/20/82	05/30/82
Hsiang-Tung Chang, China	Neurophysiology, Shanghia Brain Research Institute, Acad. Sinica	05/01/82	08/30/82
Gaetano Salvatore, Italy	Endocrinology Istituto di Patologia Generale	06/14/82	09/24/82
G. P. Talwar, India	Biochemistry All India Institute of Medical Science	06/30/82	09/30/82
Sanford Palay, United States	Anatomy, Harvard Medical School	07/01/82	09/01/82
Mordechai Sokolovsky, Israel	Biochemistry, Tel Aviv University	07/01/82	12/22/82
Lars Svennerholm, Sweden	Neurobiology, Psychiatric Res. Center Gothenburg University	08/23/82	12/22/82
Keith Porter, United States	Cell Biology, University of Colorado	09/01/82	12/15/82
Frits Orskov, Denmark	Microbiology, Int'l Excherichia Centre	09/10/82	12/15/82
Susan Lowey, United States	Biochemistry, Brandeis University	09/13/82	12/13/82
Frank Fenner, Australia	Virology, Australian National University	09/16/82	02/16/83



support for a meeting in Sweden in June 1982. Scientists from North America, seven European countries, South Africa, and Malaysia participated. Recognizing that research on the molecular biology of Chlamydia is not well advanced and that a need exists for greater knowledge of the structure and function of this pathogen, investigators believe that a better understanding could aid in improving diagnostic techniques, which are absolutely necessary to combat the infection.

Recent advances in hybridoma technology, as well as in standard classical immunochemical methods, were reported at the symposium and gave a clearer picture of the surface antigens of Chlamydia. It is hoped that these advances will lead to better diagnostic methods. Genetic studies using recombinant DNA technology were presented. The meeting also covered perinatal infections and maternal complications, eye diseases, and preventive and control measures.

### The Third World Conference on Lung Cancer

Smoking is associated with lung cancer and a host of other diseases, including cancers of the oral cavity, pharynx, larynx, esophagus, pancreas, and bladder. Smoking is also related to heart and blood vessel diseases, chronic bronchitis and emphysema, respiratory infections, and stomach ulcers. In summary, smoking is the single most important preventable cause of death and disease in our nation.

If present trends in smoking continue in the United States, lung cancer will probably be not only the leading cause of cancer death among men, but also among women.

Lung cancer is an international health problem. The FIC and the NCI provided sponsorship and partial funding for the Third World Conference on Lung Cancer held in Tokyo, Japan, in May 1982. Representatives of 27 nations served on the international program committee. The conference itself addressed a broad range of topics including prevention of lung cancer. The epidemiology, carcinogenesis, early diagnosis and staging, pathology, surgery, radiotherapy, immunotherapy, cellular kinetics, and lung tumor markers were actively discussed.

The conference theme was a succinct evaluation of current knowledge related to prevention, diagnosis, and treatment of lung cancer, focusing on both the causes of failure and the successful ingredients in the various program areas. Emphasis was placed on new approaches supported by ideas that evolved from the interaction among specialists from different countries.

### Fourth International Symposium on Nasopharyngeal Carcinoma

The causes of cancer have been the focus for much biomedical research in the past few

decades. The varying components of lifestyle, e.g., nutrition, environmental factors, are being analyzed to identify and classify significant risk factors. (A risk factor increases the incidence of a specific disease and provides an opportunity for disease prevention by intervention or by elimination of the factor.)

Nasopharyngeal carcinoma is a malignant neoplasm that has its origin at the surface epithelium of the nasopharynx. This cancer has attracted worldwide attention because of the evidence suggesting that multiple factors, including environmental, genetic, and viral, interact in the etiology of this medically interesting disease.

The FIC and the NCI provided sponsorship and partial funding support for a symposium on nasopharyngeal carcinoma held in Kuala Lumpur, Malaysia, in September 1982. Malaysia and the surrounding areas in Southeast Asia (Singapore, Hong Kong, China, and Taiwan) have a high incidence of this disease. Participants discussed the various facets of the disease: clinical, epidemiological, virologic, immunologic, and genetic, as well as treatment and prevention. Diet, chemical carcinogens, and infectious agents were examined. A wealth of evidence from studies from many countries implicates the Epstein-Barr virus. (This virus, extremely common in the human population, is clearly the cause of infectious mononucleosis.) The virus is thought to act in concert with other factors, such as immune depression and genetic factors.

### Scholars-in-Residence Program

The purpose of the Scholars-in-Residence Program is to enable established scientists and scholars interested in international health to exchange information and ideas with other scientists and scholars through preparation of a book, monograph, or other report, as well as through meetings and workshops, and to collaborate in research in an environment conducive to innovative approaches to international health issues.

Scholars-in-Residence are nominated by NIH scientists or former Fogarty Scholars. A Scholars Advisory Panel of senior intramural scientists reviews the nominees, after which approved nominees are invited by the FIC as openings in the program become available.

Since 1970, 100 Scholars from 21 countries have participated in the program. During FY 1982, 25 Scholars participated for varying periods of time, as shown in table 3-1. The average stay of the Scholars was 3 months, with 21 Scholars being in residence 6 months or less, 2 Scholars for 8 months, and 2 Scholars for 10 or 12 months each.

The following two situations illustrate the way the Fogarty Scholars interact and share their

extensive knowledge with NIH scientists:

- Professor Giorgio Bernardi used the first two terms of his scholarship to work in the Laboratory of Biochemistry, NCI, where he collaborated with the laboratory chief. Professor Bernardi is one of the international leaders in the field of gene structure at the molecular level. Much of his work is concerned with so-called "repetitive sequences" in DNA. The significance of the regulation and expression of DNA in health and disease is just beginning to be understood, but it is suspected that they are involved in modulating genetic information during development and tissue differentiation. Knowledge of this process may have implications for understanding tumor growth. Professor Bernardi's lifelong work has been concerned with the structure of large molecules such as proteins and nucleic acids. He has contributed to the methodology of this field that is important for much of contemporary molecular biology.

The benefit to the NIH of Professor Bernardi's residency has been his presence in a major laboratory, his organization of the conference on "Highly Repeated DNA Sequences in Eukaryotes" (in collaboration with his host laboratory chief at the NCI, and attended by leading researchers in molecular biology and genetics), and the opportunity afforded him to reflect on the meaning of work done over many years.

- Professor Lars Svennerholm is a world authority on neurochemistry. Dr. Svennerholm has described many of the formal components of brain and nervous tissue, such as gangliosides and other fat soluble compounds of sugar and fatty acids. These compounds have been shown to be important as parts of receptors that build antigens. There are reports that measles virus nucleotide sequelae are found in multiple sclerosis plaques from patients dying of MS. During his stay at the NIH, Professor Svennerholm initiated collaborative investigation of the hypothesis that gangliosides may be involved in formation of human brain lesions since other investigators have discovered that gangliosides produce neurological symptoms in animals. A three-way collaboration began between the neurochemistry laboratory headed by Svennerholm in Gothenburg, Sweden, the VA Hospital and UCLA in Los Angeles, and Svennerholm's NIH associates. The discovery that gangliosides (sugar-containing lipids) are receptors, or attachment sites, for various bacterial toxins and viruses, will have application to the study of cancer, influenza, and other diarrheal diseases.

The FIC scholarship played a key role by permitting Professor Svennerholm to extend his research through collaboration with U.S. scientists. This episode in Svennerholm's career exemplifies the kind of benefit that can be achieved from an extensive period of direct scientist-to-scientist interaction.

Scholars-in-Residence are provided an opportunity to organize scientific meetings and workshops during their residency at the NIH. Some examples follow.

- During Professor Svennerholm's residency at the NIH, in collaboration with colleagues from the NINCDS and the NIADDK, he organized an International Workshop on Gangliosides, which was held at the NIH in December 1981. This workshop brought together researchers in virology, oncology, biochemistry, immunology, and genetics.
- Structure and Regulation of Connective Tissue Genes. This meeting was organized by FIC Scholar Dr. Klaus Kuhn, Max Planck Institute of Biochemistry, Munich, with scientists from the NIDR, the NHLBI, and the NCI. The first session considered the structure of genes; the second was devoted to human genes and genetic disorders; and the last dealt with regulation of collagen gene expression. Dr. Kuhn expects to publish a report on the conference in 1983.
- Coexistence of Neuroactive Substances in Neurons. The proceedings of this conference--which was arranged by FIC Scholar Dr. Sanford Palay, professor of neuroanatomy at Harvard, and a colleague--will be published in 1983 by Springer.

Other Scholars interacted with their fellow scientists at the NIH in similar ways. Dr. Barondes, for example, spent time with members of the NCI Molecular Biology Laboratory, studying behavior of slime mold cells when they touch each other. For neuroscience, the study of how slime molds reproduce has implications for behavior of nerve cells, how they grow and organize themselves into networks during development.

During 1982, there were several publications by Scholars who had completed their scholarships in previous years. One such publication, Recent Advances in Mucosal Immunity, Raven Press, 1982, is the report of a meeting organized by Lars Hanson, one of the editors and major contributors who based his contributions to this effort on work performed at the NIH and in Sweden, analyzing results obtained in field studies in Pakistan on diarrheal disease in malnourished children. Dr. Hanson, who is professor of clinical immunology at Gothenburg,



continues his association with FIC activities and will participate in an FIC meeting on poliomyelitis.

The Scholars, whose interests touch on programs of every BID, also participate regularly in intramural research seminars conducted by the Senior Science Advisor to the Director, NIH. In addition, they give their own lectures and seminars. A partial list of those that took place during FY 1982 follows:

- Regulation of the Cellular Response to Hormones: Signal Propagations and Attenuation (Dr. Shmuel Shaltiel)
- Accretion of Gangliosides in the Brain During Development (Dr. Lars Svennerholm)
- Hydrophobic Chromatography Use in the Resolution and Purification of Proteins and Cells (Dr. Shmuel Shaltiel)
- Hydrophobic Chromatography: Proposed Mechanism and Its Relevance to Biorecognition (Dr. Shmuel Shaltiel)

Other conferences organized through collaboration between FIC Scholars and NIH intramural scientists were:

- Workshop on Hemoglobin Assembly and Catabolism. Organized by Professor Franklin Bunn, of Harvard University (while a Fogarty Scholar-in-Residence), in conjunction with an intramural scientist from the NIADDK, this workshop investigated the problems of hemoglobin and hemoglobin-related inherited blood diseases. These diseases include thalassemia (in which too little hemoglobin is produced), which results in anemia. Abnormal hemoglobins (the oxygen-carrying portion of the red blood cell) are a serious health problem throughout the world; recently developed technology for growing erythroid cells and other new tools of molecular biology provide new research opportunities for understanding the normal and the diseased states.
- International Workshop on the Influence of the Environment on Leukemia and Lymphoma Subtypes. Organized by FIC Scholar Dr. Bracha Ramot, professor of medicine at Tel Aviv University, this meeting brought together experts from around the world to discuss the epidemiology of lymphoid neoplasia in the light of modern immunological concepts of these diseases.
- Translational/Transcriptional Regulation of Gene Expression. This conference was organized by FIC Scholar-in-Residence Dr. Marianne Grunberg-Manago, professor of

biology at the Institute of Biology in Paris. She and a colleague at the NHLBI, Dr. Brian Safer, edited the proceedings, which were published by Elsevier in September 1982.

- Endogenous Lectins May Play Many Roles (Dr. Samuel Barondes)
- The Structure of Collagens and Errors in Their Macromolecular Organization in Some Connective Tissue Diseases (Dr. Klaus Kuhn)
- Metabolic Interconversion of Fructose Biphosphatase in Yeast (Dr. Helmut Kolzer)
- An Approach to Diabetes Health Care in Sweden (Dr. Rolf Luft)
- Immunological Approaches to the Control of Fertility (Dr. G.P. Talwar)
- Muscarinic Receptors in the Endocrine System (Dr. Mordechai Sokolovsky)

Fogarty Scholars-in-Residence and NIH intramural scientists also collaborate in the arrangement and presentation of seminars. Of the 12 seminars that took place in FY 1982, the following are illustrative: "Mechanisms for Synthesis and Inactivation of Peptides," "Molecular Mechanisms of Brain Receptors," "The Cooperative Oxygenation of Hemoglobin," "Red Cells Are Not Created Equal: The Consequences for Sickle Cell Anemia and Malaria," "Chemical Mechanisms of Action of Insulin," and "Dual Information Coding in Retinal Ganglion Cells: Small Eye Movements and Visual Acuity."

## Foreign Scientists Assistance

The Foreign Scientists Assistance Programs of the FIC provide coordination, guidance, and facilitative services to the NIH BID's in the administrative management of the NIH Visiting Program and the NIH Guest Researchers Program. These programs offer the opportunity for talented scientists throughout the world to engage in collaborative research with NIH scientists. Through these programs, the NIH is able to take advantage of the research services of over 1,400 scientists from about 60 countries. The FIC staff also supports visiting programs of the National Center for Drugs and Biologics (NCDB) of the FDA, and the National Institute of Mental Health (NIMH) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA).

Under the NIH Visiting Program, foreign researchers are invited to NIH laboratories by a

senior investigator and usually stay from 1 to 3 years. The relationship between the NIH scientific community and its foreign colleagues is based on mutual benefits; the Visiting Program is both a learning and a sharing process whereby benefits accrue to each side. Foreign scientists join NIH laboratories for a limited time to meet programmatic needs and are provided the opportunity to explore promising leads--with limited investment from the NIH. The foreign scientists enjoy enhanced capability from exposure to modern research methods for effective research in their chosen fields upon return to their home institutions.

The NIH Visiting Program has three levels: Visiting Fellow, Visiting Associate, and Visiting Scientist. The Visiting Fellows, those whose postdoctoral experience in medicine or health science does not exceed 3 years, receive awards for advanced research experience. Their scientific potential comes to the attention of NIH senior investigators through their presentations at meetings, workshops, etc., and through their contributions to scientific literature. The mid-level Visiting Associates have between 3 and 6 years of postdoctoral experience and the necessary knowledge to further a particular study. At the top level are the Visiting Scientists with more than 6 years of postdoctoral experience and exceptional abilities that enable them to make a significant contribution to the ongoing research of the sponsoring BID. Like Visiting Associates, Visiting Scientists are appointed for the performance of services for the NIH. In all instances awards and appointments are made on an invitational basis only.

The total NIH Visiting Program participation for all BID's (including NIMH and NIAAA of ADAMHA and FDA's NCDB) served by the Foreign Scientists Assistance Programs in FY 1982 was 1,523 individuals, including 1,093 foreign scientists from 56 countries. There were 749 Visiting Fellows, 192 Visiting Associates, and 152 Visiting Scientists at a cost of \$17.2 million of intramural research funds, an increase of 268 individuals over the FY 1981 total of 1,255 and an increase in total funding of \$1.4 million.

In addition to administering the NIH Visiting Program, the Foreign Scientists Assistance Programs provide advisory services in varying degrees, particularly in immigration matters, to other foreign scientists at the NIH. In FY 1982 the Foreign Scientists Assistance Programs assisted 430 other foreign scientists of whom 77 percent were Guest Researchers, who are usually funded from sources within their home countries; 10 percent were appointed as special experts funded by the BID's; and 13 percent represented scientists on bilateral agreements, FIC International Research Fellows located at the NIH, and Fogarty Scholars.

Most of these foreign scientists were from Europe and Asia, with a number from the Latin

and other North American countries, and the African and Middle Eastern countries.

Illustrative descriptions of projects in which Visiting Scientists and Foreign Guest Researchers have been involved are provided throughout this report, in the sections that describe each of the BID programs.

## International Research and Awards

Several types of international fellowship programs are supported fully or partially by the FIC and are administered by the FIC. These programs facilitate the exchange of research experiences and information by enabling foreign scientists to pursue their research interests in U.S. laboratories or, conversely, by providing opportunities for U.S. researchers to work in foreign laboratories. These programs are:

- International Research Fellowships,
- WHO/NINCDS/FIC International Neurosciences Fellowships,
- WHO/NIAID International Tropical Diseases Fellowships, and
- Senior International Fellowships.

Listed below are four other fellowship programs for U.S. scientists to study abroad, administered by the FIC but supported by the Governments of France, the Federal Republic of Germany, Sweden, and Switzerland:

- French National Institute of Health (INSERM) Fellowships,
- Alexander von Humboldt Foundation Fellowships,
- Swedish Medical Research Council Fellowships, and
- Swiss National Science Foundation Fellowships.

Under individual cooperative agreements, the FIC administers health scientist exchange programs with five countries: France (CNRS), Poland, Romania, the U.S.S.R., and Yugoslavia. NIH participation in the Special Foreign Currency (P.L. 480) Program is administered by the International Research and Awards Programs. Each of these programs is discussed in detail in the following section.

### International Research Fellowships

The International Research Fellowship (IRF) Program provides opportunities for postdoctoral



biomedical or behavioral scientists in the formative stages of their research careers to extend their research experiences in a laboratory in the United States. These fellowships forge relationships between distinguished U.S. scientists and qualified scientists in other countries to resolve health-related problems of mutual interest.

During FY 1982, there were 47 participating countries with Nominating Committees. Thirty-four Nominating Committees recommended 127 applicants for the program. Subsequent to scientific peer review conducted by the NIH, 94 (78 percent) were funded. Recipient countries of fellowship awards are shown in table 3-2.

Table 3-2.--International research fellowship awards by country/area of applicants, 1982

Americas	18	Europe	50
Argentina	5	Austria	1
Brazil	5	Belgium	3
Chile	4	Denmark	3
Mexico	2	Finland	5
Peru	1	France	5
Uruguay	1	Ireland	4
		Italy	5
		Netherlands	2
<u>Africa</u>	<u>3</u>	Norway	2
Nigeria	2	Poland	4
Sudan	1	Spain	6
		Sweden	6
<u>Asia and Far East</u>	<u>18</u>	Switzerland	1
Australia	4	United Kingdom	2
India	3	Yugoslavia	1
Japan	5		
Korea	1	<u>Middle East</u>	<u>5</u>
New Zealand	3	Israel	4
Taiwan	2	Lebanon	1

In FY 1982, a Nominating Committee was formed in China, and the Nominating Committee in the West Indies was reactivated. Applications are expected from these committees in September 1983.

Examples of collaborative research activities undertaken by IRF awardees are described in the following section.

- Renal involvement in systematic lupus erythematosus (SLE) is characterized by many different clinical and morphological features. To evaluate the effects of treatment and the prognosis on different types of SLE, an IRF awardee working with a scientist from Columbia University determined the frequency and amount of immune complex deposits in the tubular basement membrane and in the interstitium from autopsy cases of renal nephritis. These findings were

correlated with (1) the degree and type of interstitial inflammation, interstitial edema and fibrosis and tubular atrophy; (2) the type, severity, and activity of glomerular lesions; (3) the degree of renal functional impairment; and (4) the long-term prognosis. The results indicate that, in renal biopsies from patients with lupus nephritis, tubular basement membrane and interstitium deposits are usually associated with more severe and active glomerular disease. Renal insufficiency is more common and more pronounced in these patients, and the long-term prognosis is considerably worse. Renal function was reasonably good in 65 percent of the cases in patients with tubular basement membrane deposits 4 years after the original biopsy in contrast to about 85 percent for patients without these deposits. These findings are of potential significance for selection of the most appropriate therapy in these patients.

- Subjecting premature babies to oxygen-enriched breathing mixtures can result in retrolental fibroplasia or retinopathy of prematurity. The high-oxygen concentration inhibits normal development of the retinal vessels by constricting them, which leads to vasoproliferation. Using the cat as an animal model for retinopathy, one IRF awardee working with a scientist from Duke University was able to determine the contributions of oxygen levels in the choroid and the iris under different physiologic and pathologic conditions. This information with further experimentation can be used to understand the various factors or changes that take place to produce dilation or constriction of blood vessels, the changes that cause retinopathy of prematurity.
- Diabetes mellitus, which is the fifth leading cause of death in the United States, has been diagnosed in over 5 million Americans and probably affects an additional 5 million people. Several lines of evidence suggest an involvement of the immune system in the etiology of insulin-dependent diabetes mellitus. One IRF awardee in collaboration with an NIH intramural scientist studied the capacity of islet cell surface antibodies to lyse human beta cells as well as other islet cells. The Fellow demonstrated that islet cell surface antibodies react with different antigens on the pancreatic islet cells and that therefore these antibodies are heterogeneous in nature. Some of the islet cell antibodies and the islet cell surface antibodies are cytotoxic for islet cells; thus, these antibodies may play a role in the pathogenesis of insulin-dependent diabetes mellitus. This research also demonstrated

that islet cell IgM antibodies can often be detected in the area of prediabetic first-degree relatives of patients with insulin-dependent diabetes mellitus and gestational diabetes (30 percent and 46 percent, respectively).

### International Neurosciences Fellowships

The International Neurosciences Fellowship Program was established in 1977 in cooperation with the NINCDS and WHO and is administered by the FIC with funds provided by NINCDS. Three awards were made in FY 1982 to scientists in China.

### International Tropical Diseases Research Fellowships

The FIC in cooperation with the National Institute of Allergy and Infectious Diseases and with the United Nations Development Program (UNDP)/World Bank/WHO Special Program for Research and Training in Tropical Diseases has established a limited number of postdoctoral fellowships in tropical diseases. Candidates for these fellowships are from countries in which the following diseases are endemic: malaria, schistosomiasis, leishmaniasis, trypanosomiasis, filariasis, and leprosy. Two awards jointly funded by the FIC and the NIAID in FY 1982 and were made to scientists from China and Egypt.

### Senior International Fellowships

The Senior International Fellowship (SIF) Program provides opportunities for established biomedical or behavioral researchers to do collaborative research in a foreign institution. SIF's enhance the exchange of ideas and information about the latest advances in specific areas of medicine, both basic and clinical. They also lead to improvement in the research, education, and clinical potential of U.S. nominating institutions, which profit from the scientists' experiences abroad. During FY 1982, U.S. institutions nominated 71 scientists for SIF's. Of this number, 29 (41 percent) were funded. Table 3-3 lists the host countries that received SIF awardees.

Examples of collaborative research projects undertaken by SIF awardees include:

- Widespread in the population, herpesvirus infections are responsible for oral and genital infections and for such infections as chickenpox and shingles. This virus is not now controlled by vaccinations. Development of suitable herpesvirus vaccines will require the identification and production of the protective antigens. An SIF awardee in

Table 3-3.--Senior International Fellowship awards by country of destination

<u>Americas</u>	2	<u>Europe</u>	25
Canada	1*	France	2*
Chile	1	Federal Republic of Germany	1
<u>Asia and Far East</u>	1	Italy	4*
Australia	1	Sweden	2
		Switzerland	4
<u>Middle East</u>	3	United Kingdom	12
Israel	3*		

\*Two scientists have collaborative research projects in two countries.

collaboration with a scientist from the Institute of Medical Microbiology in the Federal Republic of Germany studied the frequency of cytotoxic T lymphocyte precursors in lymphoid population from normal mice and from mice infected with live herpesvirus or vaccinated with inactivated herpesvirus. The Fellow was able to show that only mice exposed to live herpesvirus developed large numbers of cytotoxic T lymphocyte precursors and that inactivated virus vaccine was a poor stimulation of such cells.

Since the cytotoxic T lymphocyte response is considered important in immunity, these results would indicate that if inactivated herpesvirus is to be used as a vaccine, a suitable and safe adjuvant that can stimulate adequate cytotoxic T lymphocyte responses may be identified.

- Researchers have shown that in the rat model of streptozotocin-induced diabetes mellitus, the disease can be treated by transplantation of fetal pancreas. The major obstacle remaining before general application of this method is the problem of rejection. An SIF awardee and a scientist from the Walter and Eliza Hall Institute in Australia explored methods to prevent rejection of transplanted fetal pancreas allografts using the rat and pig as animal models. Several methods proved partially effective in diminishing rejection of allografted pancreas: (1) prolonged culture (3 weeks) of fetal tissue in 95 percent oxygen; (2) collagenase digestion of pancreas followed by short-term (4 days) culture of tissue; (3) oral administration of cyclosporin A; and (4) ultraviolet treatment of donor spleen cells.



- Detection of small amounts of biomolecules is a challenge to scientists who are studying molecules present in small amounts in various organs or body fluids. One SIF awardee, in collaboration with a scientist from the Imperial College of Science and Technology in England, attempted to develop a new methodology for sequence analysis of nanomole or less amounts of specific proteins. In one project, using a newly developed ionization technique of fast atom bombardment and a high field magnet sector mass spectrometer, the awardee was able to show that in the dephosphorylation of casein (a milk protein), the dephosphorylation proceeds with high specificity and sequentially removes up to five phosphate groups from serine residues. This methodology can be used to elucidate biochemical structures such as the various neuropeptides.

### **Special Emphasis Senior International**

#### **Fellowship Programs**

These programs have the same purpose and eligibility criteria as the SIF Program. Since these programs are administered by the FIC in cooperation with the NIAADDK and the NINCDS, the emphasis is on arthritis, diabetes, and epilepsy. During 1982, no awards were made in these programs.

#### **Foreign Government Fellowships**

Currently four countries provide fellowships for U.S. scientists to conduct research abroad: France, the Federal Republic of Germany, Sweden, and Switzerland. These are sponsored, respectively, by INSERM, the Alexander von Humboldt Foundation, the Swedish Medical Research Council, and the National Science Foundation of Switzerland. The FIC publicizes these programs and advises prospective applicants about the programs. With the exception of the Alexander von Humboldt Fellowship applications, the NIH reviews the applications for scientific merit and, afterwards, the FIC forwards the applications and summary statements to the appropriate awarding agency to make the funding decisions, whereas the Alexander von Humboldt Foundation reviews all its own applications. In FY 1982 three applications were funded under the Swedish program and five under the Swiss.

#### **Individual Health Scientist Exchange Programs**

The FIC, on behalf of the Public Health Service, administers Individual Health Scientist Exchange Programs with France, Hungary, Poland, Romania, the U.S.S.R., and Yugoslavia. The

exchange programs, whose basic goal is to expand and disseminate scientific knowledge, foster new research ideas through the promotion of scientist-to-scientist contacts. As components of broader intergovernmental bilateral agreements for cooperation in science and technology, including health, these programs serve the broad range of health interests of the PHS and the respective foreign ministries of health. They provide opportunities for health professionals to become familiar with various aspects of public health and biomedical research activities of the participating host country. By providing support for short- and long-term exchanges, the programs encourage and facilitate direct collaboration and communication between health and biomedical communities of the United States and the participating countries.

Under an agreement between the NIH and the CNRS, the two institutions support the work of U.S. scientists in French laboratories and the work of French scientists in U.S. laboratories for periods of 6 to 12 months. The type of activity undertaken with a host laboratory may include the conduct of basic or clinical research, familiarization with or utilization of special techniques and equipment not otherwise available, and/or related cooperative efforts. Each side supports 75 person-months of work annually. During FY 1982, 9 U.S. scientists worked in French laboratories, and 11 French scientists worked in U.S. laboratories.

Under an overall science and technology agreement with Hungary, a Program of Cooperation and Exchanges that was initiated in FY 1982 now provides for individual health scientist exchanges up to 12 months from each country.

- Under these programs, during FY 1982, three Polish scientists visited the United States for familiarization with vascular and abdominal surgery, surgical treatment of tracheal strictures, and micro and laser surgery in ophthalmology.
- Four Romanian scientists spent varying periods of time at U.S. universities with research interests in the following areas: electron microscopy, cancer, recent advances in understanding pain, and surgery of the spine.
- A six-member team of American neurosurgeons visited the Soviet Union to study research in new computerized CT scanning procedures and stereotactic computerized methods for treatment and removal of central nervous system lesions. During this visit, the delegation discussed and exchanged information on problems inherent in this method and on the neurobehavioral effects on behavior before and after stereotactic removal.

- One American scientist visited Moscow and Leningrad to study clinical and research work in otolaryngology. Several Soviet scientists interested in such diverse topics as immunology, interferon research, eye surgery, neurosurgery, and artificial organs visited the United States in FY 1982.
- Activities under the U.S.-Soviet Health Exchange Program were suspended mid-year in order to evaluate the program. The FIC is attempting to identify areas of excellence in Soviet science to encourage greater U.S. participation. Activities are expected to resume in FY 1983.
- Four Yugoslav health scientists visited the United States to study various phases of hospital administration and nursing.

Table 3-4 provides summary data on these exchange programs.

### Special Foreign Currency Program

Using unique financial resources, the Special Foreign Currency (P.L. 480) Program supports biomedical research, translation, and dissemination of information in the health sciences in selected countries. In India and Pakistan, U.S.-

owned "excess foreign currencies" are used. In Poland and Yugoslavia, U.S.-owned "near excess foreign currencies" appropriated to the Department of State are deposited in joint funds where they are matched by the foreign country. In Egypt, negotiation of an analogous source of funds is underway but not completed. Administered by joint boards, these funds are allocated to the NIH and to other agencies to support biomedical research of mutual interest to the United States and Poland or Yugoslavia.

These foreign currencies cannot be exchanged for U.S. dollars or other convertible currencies, nor can funds be used without the consent of the foreign government. Central National Coordinating Committees, in addition to joint boards on which the United States is represented, review technical merit and ascertain concurrence with national policies, procedures, and priorities on health and scientific issues and take into account political, economic, and other factors.

The program is collaborative in character. Research proposals must represent a joint effort of U.S. and foreign scientists within their areas of professional interest and competence and in conformity with national priorities. The program comprises projects covering a wide spectrum of biomedical and health sciences. Attempts are made to draw upon resources unique to the host country, such as cultural, ethnic, anthropological, ecological, and disease patterns. Promising

Table 3-4.--Rate of exchange of U.S. and foreign scientists since initiation of international research and awards programs

Country	Date initiated	Maximum (man-mo per year)	Average length of stay (man-mo)	FY 1982				Total U.S. scientists to country (man-mo)	Total country scientists to U.S. (man-mo)
				U.S. scientists to country no.	m-m	Other scientists to U.S. no.	m-m		
France (CNRS)	1979	75	9.5	10	53	10	55	132	184.5
Hungary	1982	12		none		none			
Poland	1979	30	3.5	none		4	5.5	21	60.5
Romania	1967	24	1.4	none		3	6.5	30.5	96
U.S.S.R.	1961	20*	2.0	7	3	7	8	309	536.5
Yugoslavia	1979	unspecified	2.3	none		4	3.5	11	9

\*The FIC instituted a moratorium on this exchange program during FY 1982. As of January 1983, the program has been resumed with a maximum of 5 man-months per country.



projects concerned with investigation of the more fundamental aspects of biomedical problems as well as clinical and behavioral science investigations and epidemiological studies are represented in the program.

#### India

In India, the Working Group on Medical and Health Sciences of the Joint Commission on Economic, Commercial, Scientific, Technological, Educational and Cultural Cooperation, established by a bilateral agreement signed October 28, 1974, has shaped and guided the collaboration with the NIH in recent years. The Fifth Meeting of the Subcommission in 1980 was notable for its shift from the repeated emphasis of previous meetings upon indigenous infectious and parasitic diseases of primary interest to the Indian Council of Medical Research and Ministry of Health (tuberculosis, leprosy, streptococcal infections, diarrheal agents, hepatitis, encephalitis, malaria, filariasis, leishmaniasis) to the inclusion of interests in molecular and cellular biology. With the intervention of the Department of Science and Technology in the Sixth Meeting of the Subcommission in December 1981, the trend toward modern biological sciences was reflected by changing the name to the Working Group on Life Sciences, Medical and Health Sciences and by designating a subgroup on medical and health sciences and a subgroup on life sciences. The latter was to stimulate research in modern biology, genetic engineering, interferon, chemo-receptor physiology, and macromolecular dynamics.

#### Pakistan

At present no projects are active in Pakistan. The past program has been modest in size as judged by the number of projects. There is neither a science and technology nor a health agreement between the United States or its agencies in Pakistan. The Director General of the Pakistan Medical Research Council visited the NIH in FY 1982. During the discussions, such areas of mutual interests were identified as cancer, infectious disease, immunology, and training, which can serve as the basis for collaboration as clinical centers under construction in Pakistan are completed.

#### Poland

The Polish program, initiated by the U.S.-Polish Joint Committee for Cooperation in the Field of Health, was established in 1962 and for several years has had as its areas of primary interests and priorities cancer, cardiovascular disease, occupational health, maternal and child health, rehabilitation, neurosciences, metabolic and endocrine disturbances, organ transplanta-

tion and nephrology, and health protection organization. The collaborative program experienced a major disruption in FY 1982 for the first time since its inception as a result of the termination of the Science and Technology Agreement and the sanctions imposed upon Poland.

With the establishment in recent years of the U.S.-Polish Joint Board on Scientific and Technological Cooperation and its Marie Sklodowska Joint Fund, the U.S.-Polish Joint Committee for Cooperation in the Field of Health, although established earlier under a separate agreement, became a virtual subsidiary as the result of the joint fund's support of health projects. The agreement that established and maintained the joint board and its joint fund was scheduled for renewal before its expiration date of December 31, 1981. To replenish the resources of the joint fund, the Department of State was planning to provide \$2 million in zlotys annually from its appropriation beginning in FY 1982 for a subsequent 5-year period to be matched equally by the Polish Government. Prevailing economic conditions were such that the Polish side found it necessary to negotiate for a portion of the deposits to be made in dollars for basic scientific supplies. During the resulting delay in negotiations, martial law intervened. Then sanctions were imposed as the result of the expulsion of the U.S. Science Attache, and the agreement authorizing the joint board lapsed. Although there are uncommitted funds apportioned for biomedical and health sciences in the joint fund, their availability remains indeterminate.

#### Yugoslavia

The present Yugoslavia program is under the auspices of the U.S.-Yugoslavia Joint Board on Scientific and Technological Cooperation, which includes the health sciences. In contrast to other joint boards, no list of priority areas has been developed for the collaborative program in Yugoslavia. A delegation of Yugoslav scientists visited the United States at the time the joint board was established to identify productive areas for collaboration. The topics suggested were medicine, biology, cardiovascular disease (especially hypertension), malignancy (including etiology, pathology, therapy, and immunology), neurosciences, hemoglobinopathy, immunology, drug toxicity, and occupational diseases. The program, as it has developed, includes many of these topics. In addition, the Republics ordinarily propose projects in keeping with their individual local priorities and emphasize economic development and short-term applicability.

The Yugoslav side usually submits a list of 15-25 health science proposals, received from the science organizations in the several Republics of Yugoslavia. The U.S. researchers and institutions also submit proposals. The joint board meets twice a year at which time it re-



views these proposals and selects projects to be funded. The joint fund is replenished annually by equal matching deposits of dinars, in the total amount of \$3.4 million, with the U.S. deposit made by the Department of State from its appropriation. The DHHS is allotted 11 percent of this money, which is used to fund the selected projects from the various PHS agencies.

## Egypt

In Egypt the U.S.-Egypt Joint Working Group on Health Cooperation and its Subcommittee for Biomedical Research, Infectious and Parasitic Diseases has had a major role in shaping the U.S.-Egyptian collaboration. Under its direction the NIH program underwent a transition from investigator-conceived projects representing academically oriented research interests to mission-oriented projects directed at national health goals: namely, raising citizens' health awareness; reducing infant, child, and maternal mortality rates; and reducing birth rates. Population groups for special attention are infants, children of school age and under, mothers, workers, the aged, low income, and medically underserved. In addition to undergoing a review to determine the potential for immediate contributions to the objectives and populations, projects are also evaluated for their contribution to such collateral aspects of importance as institution building, manpower training, and interrelationships with other projects.

The last meeting of the Joint Working Group and its committees was held in June 1981. The remaining excess currency funds available to the NIH were committed at the end of FY 1981. The proposed Multisector Science and Technology Project expected to provide funds for FY 1982 and the subsequent 5 years was not approved. This project was to be supported by the USAID with matching funds from the Government of Egypt and funds from Title III of P.L. 480, which formerly funded the Special Foreign Currency Program under the authorization of Title I. Authorization for use of funds from this latter source has not been provided. At a planning meeting of representatives of the Joint Working Group in August 1982 in Cairo, concern was expressed about the lack of action on the Multisector Science and Technology Project. During the subsequent visit to the United States by the Minister of Health of Egypt, the status of the existing collaboration was reviewed and plans were made for a meeting of the Joint Working Group on Health Cooperation to be held in 1983.

## Scientific Accomplishments

The program in Egypt has, however, achieved some noteworthy scientific gains. For example, it fostered the development of the eye disease and blindness research center at the University

of Alexandria in collaboration with the Proctor Foundation for research in ophthalmology of the University of California. This center evolved from a blindness registry and epidemiological studies that have shown that 4.7 percent of the rural population and 1.5 percent of the urban population in Northern Egypt have significant visual disability. At least half of the loss of vision in rural areas and one-third in urban areas is due to prevalent ophthalmias and infectious diseases that are treatable and preventable. This study has also established the role of *Chlamydia*, the causative agent of trachoma, in bronchitis, pneumonias and diarrheal diseases, which account for an excessive mortality among Egyptian children.

A molecular biology study at the Indian Institute of Science in Bangalore, India, has produced a number of theoretical conformations of DNA, among them a "left-handed molecule," which was in contradiction to contemporary thought but in subsequent experimental studies by scientists in the United States was found to occur naturally. Such information is a key to the understanding of biological processes and has application to prevention and treatment of genetic diseases.

The National Library of Medicine's Critical Review Program for writing and publishing reviews of health science topics in Poland has produced a number of widely accepted publications. A review of "Human Neutrophils" brought together the findings and concepts of the brilliant hematologic school in Krakow and of other Polish hematology schools. A summary of the biology of the human neutrophilic granulocyte, a white blood cell, is given with emphasis upon the clinical significance, especially of the non-specific resistance of people to various microbial agents and the recent research evidence of the role of neutrophils in antitumor immunity. Another Polish review, "Industrial Noise Pollution and Hearing Impairment," is a product of this program and is intended for audiologists, otolaryngologists, industrial health officers, and others such as physiatrists who need a fundamental understanding of noise and hearing problems from health, social, and economic points of view. The topics included will be of great interest to those involved in rehabilitation medicine.

## International Coordination and Liaison

International coordination and liaison (ICL) activities conducted by the FIC provide for coordination of NIH international relationships to facilitate the interaction of scientists, to assist in the exchange of scientific information, and to enhance communications between the NIH and other international offices or agencies. These activities provide policy guidance, coor-



dination, and general oversight for the participation of the NIH with other U.S. agencies in bilateral cooperative agreements between the U.S. Government and other countries.

## Bilateral Agreements

The United States is contributing significantly toward the resolution of a broad spectrum of international health problems through its domestic research and related efforts, its cooperative health relationships with other countries, and its participation in the programs and activities of international organizations, notably WHO and PAHO. Formal intergovernmental agreements may take a variety of forms, ranging from those of broad scope for educational, cultural, and scientific exchange to more specific ones in science and technology or the health fields. In some instances, a health agreement may be subsidiary to a broader agreement in science and technology. Less formal technical level agreements may also exist directly between counterpart institutes for a specific purpose. As a basis for cooperation in particular situations and circumstances, formal agreements often use special resources or form a basis for surmounting constraints of different social and political systems.

Coordination of NIH participation in all bilateral agreements that involve NIH components and scientists is a continuing responsibility of the FIC. The Assistant Secretary for Health has now designated the NIH as the lead administrative agency for bilateral programs with Belgium, France, the Federal Republic of Germany, Hungary, Japan, Poland, Romania, Venezuela, and Yugoslavia. Accordingly, ICL staff carry out this role for the NIH.

During the last decade, international health research and related activities conducted by DHHS/PHS, and particularly by the NIH, have increasingly been planned collaborative efforts and have been instituted through special bilateral arrangements. Since the first formal program was signed with Japan in 1965, more than 20 bilateral health agreements have been signed directly between DHHS officials and officials of foreign ministries of health.

At present there are 42 agreements that involve the NIH with 26 countries, among which are China, Egypt, the Federal Republic of Germany, India, Israel, Japan, Nigeria, the U.S.S.R., and various countries of Eastern Europe. The NIH participates with the following countries in broad agreements covering science and technology cooperation for which the Department of State or the National Science Foundation serves as the executive agency: Egypt, France, India, Israel, Italy, Japan, Nigeria, Pakistan, Poland, Romania, Spain, Venezuela, and Yugoslavia. The NIH occasionally participates in agreements with Argentina, Australia, Brazil, Greece, Kenya,

Mexico, Senegal, and Zimbabwe. Although the FIC has a role in the administration of bilateral agreements, the scientific content of the projects supported in foreign countries is selected by the collaborating scientists at the NIH in cooperation with the foreign scientists.

Significant events that occurred during FY 1982 included:

- The U.S.-P.R.C. Joint Science and Technology Commission Meeting, which was held in Washington on October 15-17, 1981. The Joint Commission governs the agreement under which the Health Protocol operates. The Health Protocol continues to be very active with exchanges of U.S. and Chinese scientists in the areas of cancer (NCI), infectious diseases (NIAID), and cardiovascular epidemiology (NHLBI).
- The U.S.-Federal Republic of Germany agreement for cooperation in biomedical research technology, which was renewed in September 1982 for a second 5-year term with some small amendments. A workshop in the cardiovascular area held in Bethesda in October 1981 concerned cooperative activities related to the German National Health Survey. In July 1982, the FRG Minister of Youth, Family and Health visited the NIH.
- A Memorandum of Understanding between the Ministry of Social Affairs and Health, Finland, and DHHS, which has been negotiated and is expected to be signed in FY 1983. The Secretary General of the Ministry visited the NIH in October 1981 to discuss closer cooperation in health. A draft agreement between the NIEHS and the Finnish Institute for Occupational Health was developed in FY 1981.
- The U.S.-France Science and Technology Bilateral Meeting, which took place in Washington in September 1982. Under the framework of the science and technology agreement, the NIH has a cooperative program with INSERM. Current areas of active cooperation include cancer, respiratory diseases, and thyroglobulin synthesis.
- The tenth meeting of the U.S.-Spain Joint Committee for Cooperation in Science and Technology, which was held in Washington in May 1982. This committee, a component of the Treaty of Friendship, provides for cooperation in science and technology with a recently added provision for health.
- Two agreements signed under the overall cooperative science and technology agreement with Italy: (1) by the NINCDS, in

March 1982, for collaboration in neurosciences research with the National Research Council of Italy, and (2) by the NHLBI, in November 1981, for cooperation in cardiovascular diseases with the Pharmacological Institute, University of Milan. In addition, in November 1981 under the science and technology agreement a workshop was held by the NIH in Bethesda entitled "Biological Response Modifiers," and a joint symposium by the NHLBI, "Methods of Noninvasive Diagnosis in Cardiovascular Disease."

- The July 1982 meeting of the Joint Committee of the U.S.-Japan Cooperative Medical Science Program, in Tokyo at the Ministry of Foreign Affairs. The Joint Tuberculosis Panels and Joint Viral Disease Panels have begun a review that will be completed next year. After reviewing the Leprosy and Parasitic Disease Panels, the committee recommended their continuation. In the future, the Leprosy and Tuberculosis Panels will hold combined annual meetings in view of their common scientific interests, and the guidelines for the Joint Parasitic Disease Panels will be updated to accommodate new technologies and changing needs.
- The U.S.-Mexico meeting in Bethesda in December 1981, which resulted in an agreement between the PHS and the Ministry of Health of Mexico to collaborate in research and training in infectious diseases, particularly those of children.
- The September 1982 visit to the United States by the Indian Prime Minister, which resulted in an agreement to establish an Indo-U.S. Blue Ribbon Panel to enhance science and technology cooperation between the two countries. Areas of interest being considered in the health field are leprosy, immunology, and blindness prevention. The ICL staff of the FIC work with staff of the Office of International Health and the Office of Science and Technology Policy in coordinating the programs at the NIH.

### Other Liaison Functions

In addition to monitoring and assisting in bilateral activities, the ICL staff maintain liaison with WHO and PAHO and occasionally with other multilateral organizations, and they provide NIH positions on agenda issues for World Health Assemblies and PAHO and Western Pacific Regional Organization Directing Council meetings. ICL staff also provide material and support for NIH participation as an observer in meetings of the European Medical Research Council and process requests for services of NIH

experts for WHO and PAHO committees and other purposes.

The FIC is cooperating with PAHO in organizing and sponsoring a Workshop on Research Management Techniques for Latin American scientist administrators. The workshop, aimed at directors of large research institutions, research departments of major universities, and large public health laboratories, will be held in FY 1983.

The ICL staff assist the Institutes by reviewing and clearing foreign travel plans and by serving as a channel for cable communications to and from foreign embassies and the Department of State, by coordinating responses to inquiries on international issues, and by processing NIH foreign grants and contracts for clearance through the Department of State.

The FIC Director meets periodically with the international programs representatives of the NIH BID's to exchange information and views on NIH international activities and to discuss implementation of related policies and procedures.

Information on NIH international activities is collected and published in an annual report. Special reports are prepared and made available to NIH principals traveling to certain countries and to officials from other countries who visit the NIH. In addition, comprehensive briefing books on NIH activities with various foreign countries are produced.

A special study underway in FY 1982 was a compilation of information on biomedical research institutions in China. The report, due to be published in FY 1983, will be available to all interested scientists and Government officials. It will contain names and locations of the institutions, directors and laboratory chiefs, and recent publications from these institutions.

### Gorgas Memorial Laboratory

The ICL staff also serve as the focus for U.S. Government core support provided through the FIC budget for the Gorgas Memorial Institute (GMI) of Tropical and Preventive Medicine, Inc., and the Gorgas Memorial Laboratory (GML) in Panama. In 1928, Congress authorized a permanent annual appropriation to the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., Washington, D.C., for the operation and maintenance of a research laboratory in Panama. This action, together with land and building donated by the Government of Panama, permitted the establishment of the GML. Since FY 1971, the FIC budget has provided the annual U.S. core support funds, which amounted to \$1.69 million in FY 1982. The FIC maintains general program oversight for this funding.

The laboratory conducts a diversified program of research on tropical diseases, especially those endemic to Panama and neighboring countries. Particular emphasis is placed on virology, par-



asitology, and the effects of environmental change on disease vectors and transmission. Of late, it has also undertaken studies on other public health problems, e.g., cervical cancer and sexually transmitted diseases. In addition to research, it also provides special diagnostic and reference services, epidemic investigations, and surveillance of vector-borne diseases, and it conducts formal and informal research training for scientists and technicians from the United States, Panama, and other countries. It has cooperative arrangements with several U.S. universities for graduate and medical students. Formal training courses in tropical medicine are conducted several times a year for U.S. Navy medical officers. For FY 1982, the GML had a number of substantial scientific accomplishments in the following areas:

- Ecology. The Bayano environmental ecological studies indicated significant alterations in insect vectors and disease potential in the area. Yellow fever surveillance among monkey populations in the mountainous areas of eastern Panama indicated a resurgence of sylvatic yellow fever beyond last year's limits. A manuscript on the mammalian fauna of Panama was completed, and extensive progress has been made on a compilation of the rodents of Panama. Studies describing how excessive hunting, massive deforestation, and other ecological problems have contributed to the disappearance of a number of valuable animal and plant species have resulted in recommendations for conservation of natural resources.
- Vector Biology. Work in this area has expanded markedly. Currently 255 animal and avian species have been bled in the preparation of antisera for blood meal analysis. Over 7,000 hemotophagous arthropods representing 17 genera and 88 species of sandflies, mosquitoes, triatomes, and culicoides from Central and South America have been studied. Further study of lutzomyia sandflies and of man-biting black flies (simulium quadrivittatum) has enabled GML scientists to characterize these disease vectors fur-

ther, a step necessary to future vector control efforts.

- Epidemiology. An epidemic of acute hemorrhagic conjunctivitis, which occurred in Colon in 1981, was subject to a detailed seroepidemiological study. A 53 percent clinical attack rate was found, as well as information on the effect of socioeconomic level, crowding, and other parameters. A preliminary serological study indicated 22 percent of the individuals tested had antibodies for HTLV, the highest known antibody rate for HTLV. Further studies are planned in collaboration with the NCI. Haemagogus equinus mosquitoes have been studied for their efficiency as a vector of yellow fever. Studies have shown that St. Louis encephalitis virus transmission is an annual occurrence at two ecologically distinct sites in Panama, a finding that supports field data implicating the two-toed sloth as a host for the St. Louis encephalitis virus.
- Parasitic Diseases. Drug evaluation in the Aotus monkey revealed two agents with significant antimalarial activity. Success in maintaining Plasmodium vivax for 10 days with one subculture was recorded. Field study in Morti, Darien Province, indicated an endemic focus of Mansonella ozzardi probably transmitted by simuliid flies.
- Bacteriology. Further studies on Campylobacter jejuni in childhood diarrhea indicate a high incidence in the first 6 months of life. Antibody resistance to strains of Shigella and the emergence of several new strains have been documented. Penicillin-resistant strains of gonococci were encountered in 12 percent of 377 prostitutes examined.

The GML is being reorganized to emphasize tropical ecology, epidemiology, microbiology, and clinical therapeutics. This reorganization, as well as the consolidation of facilities, will enable the GML to maintain a productive research program.

## Chapter IV

### National Cancer Institute

The international battle against cancer offers perhaps the best and most immediate opportunity for changing the basic quality of life for millions of people throughout the world. The National Cancer Institute (NCI) continues to contribute readily to the improvement of that quality of life because of its long tradition of involvement in the international arena for cancer research. Although self-interest, on behalf of the people of the United States, motivated NCI's initial concern with cancer problems in other nations, this self-interest has been transformed into a concerted international campaign in the war on cancer. The National Cancer Act intensified the commitment of the NCI to the international team approach toward the control, prevention, and ultimate eradication of cancer as a majorcrippler and killer disease of a large segment of the world's population.

By virtue of an international effort, striking geographic and environmental variations in the incidence and mortality of a wide range of specific organ cancers are now well recognized and, in some instances, environmental causes have been established for excess rates of cancer incidence in certain regions of the world. For instance, environmental factors are implicated in the causation of a large percent of the known cancers. The derivation of this cause-effect relationship stems from studies in those countries of the world where the population is at low risk for a given type of cancer, thereby establishing a "baseline" rate for that particular cancer type. Subsequently, a high rate of incidence for that same cancer in other countries can be assumed to be associated with environmental factors. That the incidence of various types of cancer exhibits great geographic variation is illustrated by differences in the rate of lung cancer incidence among men in Scotland, the United States, and Portugal. Scotland, with the highest rate in the world, has twice the rate for U.S. white males, whereas the rate among Portuguese males is one-seventh that of Scotland. Again, in the Kazakh Republic of the U.S.S.R., the incidence of cancer of the esophagus is extremely high in regions near the Caspian Sea in comparison to the low incidence in the extreme eastern section of that Soviet republic.

Through its participation in activities of the international cancer science community, the NCI benefits from rapid advances in basic research throughout the world and application of this new information to the clinical management, control, and prevention of cancer. The ultimate gain from such collaborative cancer research efforts of the NCI and international counterparts is a tangible improvement in the quality and quantity of health services available to millions of people over the world.

The contribution of the NCI to the international struggle against cancer includes: (1) continuing support of cancer research in foreign countries by highly qualified scientists; (2) support of cooperative research programs, principally under bilateral agreements with foreign governments, institutions, or organizations; (3) maintenance of liaison and research collaboration with international organizations and agencies that have well-defined objectives in cancer research and cancer prevention; (4) support of training of foreign scientists in the United States as well as of the interaction of American scientists with colleagues in foreign laboratories; and (5) management and operation of an International Cancer Research Data Bank for promoting and facilitating, on a worldwide basis, the exchange of information for cancer research, care and management of patients, and cancer control and/or prevention.

#### Summary of International Programs and Activities

##### Bilateral Agreements and Other Country-to-Country Activities

Cooperative cancer research programs under formal government-to-government treaties and other forms of bilateral agreement constitute a major segment of the international activities of the NCI. The first of these cooperative cancer research agreements was established May 23, 1972, with the signing of the U.S.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Science and Public Health. Subsequently, additional bilateral programs were formalized between the NCI and the Japanese



Society for the Promotion of Science (1974); the Institute of Oncology, Warsaw, Poland (1974), under the U.S.-Polish People's Republic Agreement; in 1975 with INSERM, under an earlier NIH agreement with INSERM; the Cairo Cancer Institute (1976), under the aegis of the agreement between the United States and the Arab Republic of Egypt; the Ministry of Science and Technology of the Federal Republic of Germany (1976); the Cancer Institute (Hospital), Chinese Academy of Medical Sciences, under the U.S.-P.R.C. Accord for Cooperation in Science and Technology (1979); the NCI of Milan and the Institute of Oncology of Genoa, Italy (1980); and the National Institute of Oncology, Budapest, Hungary (1981).

The following sections describe NCI bilateral activities and the progress that has been made through these cooperative efforts.

## China

Between January 1, 1981, and October 30, 1982, seven American scientists visited institutes in China to hold consultations, to present lectures, to provide technology demonstrations, and, generally, to enhance the exchange of data and information on cancer research topics of mutual interest and benefit. Reciprocally, seven cancer specialists from China participated in study/research programs and scientific workshops at the NCI and other American cancer centers. These exchanges have effectively furthered the development and implementation of joint research activities on cancer problems of mutual interest, with a number of channels of communication and a variety of mechanisms in use.

Collaboration under Annex Two of the Health Protocol.—Pursuant to the provisions of Annex Two, the NCI received two epidemiologists, each for 1 year of study/research. A third Chinese specialist, an endoscopist/diagnostician, came for 1 year of observation and experience in the clinics and laboratories of selected American cancer centers.

The Cancer Institute (Hospital), Beijing, was the coordinating focus for the activities of two NCI scientists, each for 1 month of exchanges, relating to the subject of early detection and diagnosis of cancer.

Direct interinstitute collaboration (outside of the Annex).—This approach, endorsed by the Program Coordinators, has permitted additional scientific exchanges and project development.

- Two American specialists in anticancer drug development and evaluation, one from the NCI and one from the Mid-American Cancer Center in Kansas, visited Chinese cancer and pharmaceutical institutes for exchange

of information and technology related to development of anticancer preparations, especially products of natural origin. An American surgeon lectured on current procedures and techniques for the detection, diagnosis, staging, and surgical treatment of esophageal and pulmonary carcinomas.

- Two joint research projects have evolved as a result of informal exchanges, in early 1980, between an NCI intramural scientist and his colleagues of the Beijing Cancer Institute (Hospital). They are studying the biochemical epidemiology of esophageal and liver carcinogenesis, with emphasis on the effects of carcinogen-DNA adducts.
- An epidemiologist and a chemotherapist from the Beijing Cancer Institute (Hospital) and an immunopathologist from the Shanghai Cancer Institute participated in a 2-week NCI workshop entitled "Epidemiology of T Cell Lymphomas and Leukemias." As a result of these exchanges, a multidisciplinary research project is under consideration for implementation, pending receipt of some additional data from the Chinese side.
- A contract for "Feasibility Studies for Collaborative Cancer Epidemiology Research in China" has been negotiated between the NCI and the Cancer Institute (Hospital) in Beijing. The research activities to be conducted in China include: a nutrition intervention trial and case-control study of esophageal cancer in Linxian, a case-control study of lung cancer in Shanghai, and a case-control study of choriocarcinoma, initially in Beijing, with subsequent expansion to other areas of high incidence and mortality in China.
- An outgrowth of scientific exchanges during a late 1981 and mid-1982 visit by an NCI-sponsored nutritionist/biochemist was a proposal to study the effect of dietary selenium and other trace elements on cancer risk and incidence. An NCI grant has been approved that will permit implementation of this collaboration and will include joint evaluation of the role of dietary selenium, vitamins A/beta-carotene, vitamins C and E, and other factors in cancer in both human subjects (China) and experimental animal systems.

During the coming year, under Annex Three of the Health Protocol, the NCI will receive Chinese scientists for study/research in molecular biology, clinical laboratory science, and cancer detection and diagnosis. Reciprocally, the NCI will send scientists to China for collaborative studies related to early detection and diagnosis



and to epidemiologic research. Areas considered to be of significance and mutual benefit include identification and characterization of biochemical/biologic markers of tumors, unified concepts for the collection and analysis of epidemiologic data, photoimaging and intensification in detection/diagnosis, exploitation of the utility of photoradiation therapy, and studies related to genetic predisposition or susceptibility to cancer.

The joint research efforts initiated as direct interinstitute activities will continue. Other such initiatives will be considered on a research priority basis, for instance, studies on automated cytology and dietary factors and their role in carcinogenesis and/or in cancer chemoprevention/intervention.

### Egypt

The Cairo Cancer Institute, a well-organized facility, has an accrual of patients with bladder cancer perhaps greater than that of any other single institution in the world. Recently, a Phase II study of chemotherapeutic agents for bladder cancer was completed, having been initiated in 1976. Twelve drugs were studied in about 400 patients with squamous and transitional cell bilharzial bladder carcinoma. The preparations studied included hexamethylmelamine, VM26, methotrexate, bleomycin, adriamycin, platinum, cytoxan, fluorouracil, trenimone, m-AMSA, vincristine, and pentamethylmelamine. Notable response rates were 38 percent for hexamethylmelamine, 40 percent for pentamethylmelamine, 44 percent for vincristine, and 60 percent for trenimone. The response rates for cytoxan, fluorouracil, and DDP are, respectively, 28 percent, 15 percent, and 13 percent.

On the basis of these results, an active chemotherapy combination might include vincristine, pentamethylmelamine, and fluorouracil. The durable response rate after radical cystectomy in bilharzial bladder carcinoma is 35 percent (5-year disease-free survival), not improved by pre- or postoperative radiotherapy. The combination described above is under active consideration as are other combinations of drugs. It is anticipated that 100 patients can be entered on each arm of a two-armed randomized study within 2 years. The drugs would be made available by the NCI for this latest study under the U.S.-Egyptian program.

### France

Two broad areas of cancer research now constitute the cooperative activities between American and French cancer specialists. These are a basic cancer research program area and a clinical cancer research program area. Activities constituting the basic area include biologic and chemical carcinogenesis, cellular and molecular biology, viral oncology, cancer immunology, and

hormone research related to cancer. In March 1982, during a review and evaluation meeting, American and French collaborators agreed to continue the research programs that have been established and show promise as well as to stimulate new ideas and support the exchange of scientists for information and active research collaboration. Thus, five American investigators subsequently spent periods ranging from 2 weeks to 6 months in French laboratories for collaborative studies in hormone and receptor research, nucleic acid metabolism and alteration, mutagenesis, and carcinogenesis. Reciprocally, four French investigators worked in American laboratories on research problems related to gene expression, hepatitis virus antigens, viral oncology, and antiviral interventions in certain types of cancers.

In Paris, in June 1982, the joint American-French Committee for Clinical Cancer Research met to review the progress that had been made in that area as well as to plan the program for the subsequent year. They assessed cooperative research endeavors in the clinical study of breast cancer treatment, the treatment of osteosarcoma, biochemical and clinical pharmacology, and hormone therapy used in breast cancer. An American epidemiologist spent 6 months collaborating with French investigators on biostatistics and clinical epidemiology. An American endocrinologist spent 2 weeks in France conferring with experts on the biochemical effects of estrogens in endometrial cancer, while a French pharmacologist came to the United States to receive advanced training in biochemical pharmacology so that he could establish a collaborative research program with his American colleagues upon his return to France.

### Federal Republic of Germany

In the environmental carcinogenesis program area, an epidemiologist from the German Cancer Research Center in Heidelberg visited the NCI to exchange information on analytic epidemiology and to engage in a case control study of occupational epidemiology related to workers in certain hazardous occupations. He was able to accrue experience in the conceptual aspects of epidemiologic investigations, data analysis, and the implementation of studies in the network of surveillance and monitoring. Based on his exchanges in the United States, at the NCI and New York University Medical Center, he and his German colleagues are involved with American counterparts in the development of joint epidemiologic studies of workers in the chemical industry. Included in the joint effort will be the establishment of a system for cancer registry.

A German pathologist came to the NCI to conduct joint studies aimed at developing a common system of classification and terminology related to experimental cancers and tumors



so that a comparable system could be established in the NCI and the German Cancer Research Center in Heidelberg. Thus, an exchange of materials and specimens for comparative studies between the Federal Republic of Germany and the United States will now be possible.

### Hungary

Three American immunologists visited Budapest to attend a course, "Highlights in Modern Immunology," sponsored by WHO and the Hungarian Society of Immunology. The course, consisting of lectures delivered by members of the Hungarian Society and other internationally renowned scientists, addressed topics relevant to immunogenetics, immune receptors, effector functions and their regulation, and differentiation. The lectures were aimed at young scientists and were, therefore, broad in nature. The consensus of the Americans was that, in general, the Hungarian immunologists with whom they interacted were impressive and that these Hungarian scientists appeared to be very eager to continue and to further expand the scientific exchange of information with Americans.

An intramural NCI scientist spent 2 weeks in Budapest participating in exchanges of information on theoretical and practical concepts in pathology and cancer data processing. As well, he hoped to determine if the methods of pathology data processing used in Hungary have application in the United States.

An experimental chemotherapist from the National Institute of Oncology, Budapest, spent 6 months in the NCI Laboratory of Medicinal Chemistry and Biology engaging in studies designed to investigate the resistance of murine tumor cells to alkylating agents used as anticancer drugs. Her work and that of her NCI colleagues have confirmed the role of the tripeptide glutathione in resistance of tumor cells to alkylating agents. These studies have demonstrated that it is possible to sensitize the resistant cancer cell completely to the cytotoxic effects of an anticancer drug such as L-phenylalanine mustard, commercially known as Melphalan. Melphalan is one of the effective drugs, used in combination with others, for the treatment of breast cancer. Additionally, the chemotherapist devoted considerable effort toward the development of amino acid specific, synthetic-pelleted diets for use in these experiments. She contributed significantly to the evaluation of an Alzet osmotic minipump for continuous intraperitoneal infusion of agents such as buthionine sulfoxime (an inhibitor of glutathione biosynthesis) and anticancer agents, thus affording a concentrating effect of antitumor agent at the site of the cancer.

A transplantation biologist/tumor immunologist from the National Institute of Hematology and Blood Transfusion, Budapest, spent 4 months

in the Sidney Farber Cancer Institute (SFCl). He devoted his efforts there to joint research on developing monoclonal antibodies active against T cells and monocytes in endothelial cells (EC). His approach was to collect endothelial cells from the umbilical cord and to enmass the antigens acting against the monoclonal antibodies. Based on his research, he concluded that EC are rich in their expression of HLA-A, B, and C antigens but that their expression of HLA-DR is anomalous. EC also share myelomonocytic surface antigens, My-7, Mo-3, and Mo-4. The relevance of these findings to transplantation is enhanced by initial observations that Mo-4 is also expressed in human kidney endothelium as shown by immunoperoxidase reactions. The researcher became acquainted with the method for phenotyping leukemic cells by means of monoclonal antibodies and, by virtue of an SFCl gift of a series of monoclonal antibodies, he has begun phenotyping leukemias and lymphomas in his laboratory in Budapest. Because of the SFCl interest in the Hungarian study on HLA-antigen distribution in gypsies and in the incidence of various diseases in this ethnic group, the Hungarian scientist has provided SFCl scientists with more than 30 blood samples of Hungarian gypsies for typing the complement phenotypes.

An experimental pathologist/chemotherapist from the Semmelweis Medical University in Budapest spent 6 months at the Roswell Park Memorial Institute to study methods of tumor disaggregation--mechanical and enzymic--to yield single cancer cell suspensions. At the same time, he developed cell separation methodologies for biochemical, biologic, and morphologic characterization of the various tumor subsets derived from the human tumor cell suspensions. The subsets, then, were tested for their sensitivity to anticancer drugs. Among 17 tumor cell types studied, there were significant differences in the number of cells obtained by disaggregation. In six cell fractions, intracellular concentration of the anticancer agent, Ara-C, and <sup>3</sup>H-thymidine was higher in the fractions containing more viable cells. The effect with a platinum-derived drug was the opposite, in that results suggest an intensive binding to nonviable cells.

### Italy

Activities in cancer therapeutics and cancer prevention constitute the efforts of collaboration between American and Italian cancer specialists.

During the annual review meeting for the cancer therapeutics program, held in Bethesda, Maryland, in November 1981, there was a detailed exchange of information in the areas of clinical trials, basic and clinical pharmacology, and cancer related epidemiology. Until now, the need to establish a foundation for a collaborative



project in biochemical pharmacology, breast cancer treatment, pediatric oncology, cancer metastases, clinical trials with anthracyclines, radiation oncology, and biologic response modifiers has motivated the joint workshops and symposia. In the next year, it is anticipated that specific joint projects in clinical and preclinical cancer research will be defined.

Two American pharmacologists from the Roswell Park Memorial Institute visited Italian research centers to discuss and plan collaborative research on the study of modal systems for investigating drug metabolism and to obtain the most recent information on the anthracycline drugs being tested and used in Italy.

From the Italian side, a pediatric oncologist observed the methods of treatment for childhood cancer in cancer centers of the United States. Another pediatrician spent 2 months at the NCI to participate in a study of Phase I and II drugs being used to treat solid tumors and acute lymphoblastic leukemia in children. He was also a benefactor of the latest information on dose-limiting toxicity and antitumor activity of those drugs being used currently to treat bone sarcomas, neuroblastoma, and other childhood cancers. An immunologist from Italy spent 2 months at the Frederick Cancer Research Facility to study the utility and physiologic effects of biologic response modifiers currently in use to treat cancer. Advanced training in biochemical pharmacology and experimental chemotherapy was the goal of a young Italian oncologist who spent 1 year of study/research at the Roswell Park Memorial Institute in Buffalo, New York.

The annual review meeting for the cancer prevention program took place in conjunction with the "Workshop on Leather, Benzene, and Shipyard Workers," which was convened in Portofino, Italy, in 1981. The workshop was devoted to discussions on the development of collaborative studies for identification of environmental determinants of specific cancers. Unique opportunities exist in Italy to assess the impact of certain occupational exposures, particularly benzene, chromates, and dusts in the leather and shoemaking industries. Attention was focused, as well, on the risk of lung cancer among shipyard workers.

An Italian viral oncologist spent more than a year at the Mount Sinai Medical School in New York to study the relationships between polyamine biosynthesis and differentiation in an attempt to elucidate the biologic role of these compounds in the steps leading to differentiation of the erythroleukemia cells.

An Italian biochemist spent 3 months at the M.D. Anderson Hospital and Tumor Institute in Houston, Texas, to learn techniques for the detection of alterations in DNA induced by carcinogens. As a result of this interaction with his colleagues, this researcher participated in

devising plans to continue the collaborative studies initiated on the differential and systematic enzymatic digestion of DNA and on the separation and analysis of the subsequent DNA fragments.

## Japan

At the outset of the agreement between the NCI and the Japanese Society for the Promotion of Science, 11 specialty areas in cancer research were pursued jointly. Three years ago, these were categorized into four broad program areas, namely, etiology, cancer biology and diagnosis, cancer treatment, and interdisciplinary research.

Cancer epidemiology, chemical carcinogenesis, viral and biologic carcinogenesis, and molecular biology constitute the principal areas of research being pursued under the etiology program. The principal objectives are to clarify the cause of human cancers and to determine the mechanism(s) of carcinogenesis.

During the course of a seminar entitled "Carcinogenesis and Gene Expression in Liver Cell Cultures," held in Hawaii in November 1981, information was exchanged on the patterns of expression of various genes during carcinogenesis, especially hepatocarcinogenesis. Data presented at the seminar indicated that changes in the expression of various genes were reflected by the production of enzyme systems and other proteins that were not found in the normal liver cell. The change is so pleiotropic that the mechanisms of some of these changes would be intrinsically relevant to the carcinogenic process.

Many aspects of intestinal metaplasia were considered during a conference titled "Intestinal Metaplasia and Stomach Cancer," convened in Shimodu, Japan, in March 1982. New histologic and biochemical enzymatic techniques were considered as were new methods for histochemical and immunologic assays. An interesting finding emerged with bearing on the relationship between mesenchymal and epithelial tissue, namely, that stroma can influence and guide the development of epithelial tissues. Although there was no consensus on whether intestinal metaplasia is a precursor lesion for stomach cancer or only an associated condition, some investigators believed that a definite precursor relationship could be demonstrated. Since the cause of stomach cancer is complex, it is reasonable to expect that some stomach cancers can be formed by a process not related to the formation of intestinal metaplasia.

A conference entitled "Cell Interaction and Cancer," held in Kyoto, Japan, in November 1981, was one of the focal activities in the cancer biology program area. Information was exchanged between American and Japanese counterparts on a diverse series of topics ranging from cell-to-cell adhesion in primitive cell



systems to studies of the pathology and biology of human cancer cells. Highlighting the discussions was the study of differentiation of tissue mast cells and the growth of leukemia cells in microenvironments; cell-binding sites of collagen, heparin, and other macromolecules; and regulatory proteins on transformed cells.

In another activity in this program area American and Japanese immunologists convened a meeting in Boston in November 1981 on the analysis of mechanisms for induction of tumor-specific immunity and experimental approaches to tumor immunoprophylaxis and therapy. The participants focused their attention on the antigenic nature of tumor cells, expression and regulations of tumor antigens, fundamental immunologic processes in host response to tumors, and preclinical applications of tumor immunology.

Hakoni, Japan, was the site in March 1982 of a meeting on the application of cytology automation in cancer cytology and cell biology, as a component of the cancer diagnosis program area. American and Japanese investigators discussed the latest information on instrumentation and data analysis, the application of automated cytology technology in cell biology, a new technological approach for sample preparation, and the application of automated cytology in cancer detection.

It was a particularly active year in the cancer treatment program area in which three meetings were convened. The first, the Seventh Annual Program Review Meeting, related to development and evaluation of treatment of cancer with combined modalities of therapy. The conferees were concerned with three topics: treatment of oat cell carcinoma of the lung in the United States and Japan; development of new methodology in clinical and preclinical investigations, including the progress of human tumor cloning assay as a predictor for the sensitivity *in situ* of human tumors to administered drugs; and new antitumor agents, natural and synthetic, now in Phase I and II as well as those still in preclinical stages of development.

The second assembly in this program, which took place in October 1981 in Maui, Hawaii, was the first meeting on preclinical and clinical trials of tumor immunology. Subjects for information exchange included experimental studies of cancer immunotherapy, possible application of human T cell hybridomas for immunotherapy of cancer, monoclonal antibody therapy in man, adjuvant immunotherapy of lung cancer with bacterial cell wall skeleton preparations, current status of interferon therapy, and clinical trials using immunotherapeutic approaches.

The third meeting, held in Tokyo in November 1981, concerned advances in the treatment of bladder cancer. Topics for information exchange were superficial cancer of the bladder, deeply invasive cancer of the bladder, metastatic

disease, prevention of bladder cancer, conduct of clinical trials, and projected cooperative bladder cancer treatment programs. In general, the exchanges served as a foundation for further cooperative studies of bladder cancer as well as basic and clinical investigations on bladder cancer. In addition, criteria for diagnosis and for development of protocols were established, which will be useful to investigators in both countries for facilitating the mutual understanding and use of diagnostic, therapeutic, and clinical technologies.

In Hawaii, in March 1982, a seminar entitled "Neural Crest Tumors" represented a key activity in the interdisciplinary program area. During the session, attention centered on certain syndromes associated with tumors or familial neoplasia derived from the neural crest and on differences between the frequencies of these tumors in both countries.

American and Japanese viral oncologists, pathologists, and epidemiologists assembled in Seattle, Washington, in March 1982 to discuss the nature of T cell leukemias and their probable etiologic agents. During this symposium entitled "T Cell Leukemia/Lymphoma--Role of Human Type C Retroviruses," it was learned that teams of American and Japanese virologists had independently isolated and identified retroviruses associated with HTLV and ATLV, respectively. These newly identified human retroviruses seem to be identical or very similar to each other. The viruses are closely associated with mycosis fungoides, Sezary syndrome, and adult T cell leukemia that belong to the category of differentiated T cell lymphoma and leukemia. The viruses have been found to be endemic in the southwestern part of Japan and in certain Caribbean islands.

Related to the foregoing, an American pathologist visited several Japanese laboratories to review information and to plan cooperative studies on leukemias and lymphomas. Reciprocally, a Japanese scientist came to the United States to visit cancer centers for the study of the classification of lymphomas. Another Japanese, an immunologist, spent his time studying methods for *in vitro* sensitization and testing of cytotoxic lymphocytes.

## Poland

Exchange of scientists between the Polish People's Republic and the United States has continued to be effective, despite the current political climate in Poland.

An American pharmaceutical chemist spent 6 weeks at the Institute of Oncology in Warsaw to conduct collaborative studies in nuclear medicine and radiopharmaceutical research. With his Polish counterpart, he investigated the possibilities of using microspheres as carriers of



radioactive isotopes for treating certain types of cancers such as hepatic carcinoma. The experiments demonstrated the stability of microsphere carriers in animal models as well as the potential for the use of such agents in treating cancers in humans.

During the year, six Polish scientists visited the United States to do research in their specialties. The first, a tumor biologist, visited centers of excellence in the United States to exchange information and learn of recent advances in radiation biology, cancer immunology, and biology. A biologist from the Institute of Oncology in Warsaw spent 6 months collaborating on DNA polymerase research at the Roche Institute of Molecular Biology. A Polish biochemist came to do research on chemical carcinogenesis. A pharmacologist spent his time in collaborative studies of biochemical pharmacology and tumor immunology at the Roswell Park Memorial Institute.

The director of the Institute of Oncology in Warsaw, after attending the 13th International Cancer Congress in Seattle, Washington, visited cancer centers in that area, as well as others in the United States, for discussions on the progress and achievements of the Polish National Cancer Program as well as the accomplishments under the U.S.-Polish People's Republic Cooperative Cancer Program. Finally, a pediatrician from the Nation Research Institute of Mother and Child in Warsaw observed and studied treatment modalities and procedures for childhood cancer in the Pediatric Oncology Branch of the NCI.

#### U.S.S.R.

The six original program areas -- in effect since inception of the U.S.-U.S.S.R. Health Agreement in 1972 -- were modified, restructured, and/or merged during the Sixth U.S.-U.S.S.R. Meeting on the Problem of Malignant Neoplasia, held in Bethesda, Maryland, September 1981. Thus, the scientific areas of cancer treatment, carcinogenesis, and cancer prevention now constitute priority areas for continuing collaboration between American and Soviet cancer specialists.

An NCI intramural scientist, during his November 1981 visit to Moscow's All-Union Oncologic Scientific Center, was able to engage in productive discussions on cancer chemotherapy, especially from the view of detailed analyses of raw data and participation in clinical rounds for the observation of Soviet patients entered into a parallel study of tamoxifen as an adjuvant in the surgical treatment of breast cancer. Preliminary data indicate positive treatment results with this agent, and the patient accrual under the study should yield promising information regarding this mode of treatment. The NCI provides the tamoxifen and research counsel for this parallel study.

The NCI has been provided with additional quantities of the Soviet drug known as histar, for completion of preclinical testing in xenograft systems following demonstration of positive histar activity in L-1210 leukemia, B-16 melanoma, and CD8f mammary tumor. The Soviets are also preparing samples for NCI testing of three compounds of natural origin and their indication of potential use as anticancer agents. These are bacuchiol, an antibiotic, and chrysophanol and cynodontin, which are lichen products.

During their January-February 1982 visit to the NCI and other U.S. cancer centers, two Soviet chemotherapists joined American colleagues at the University of Maryland Cancer Center to design and develop a protocol for a "Phase I Clinical and Pharmacologic Trial of Platinum diammine (1,1-cyclobutane-dichloro-oxylate)2-(-0,0')." The agent is commonly referred to as CBDCA. Paralleling the study of the American scientists and clinicians, the Soviets will pursue (1) establishing the maximum human tolerable dose of CBDCA; (2) evaluating its toxicity in patients with previously treated and untreated malignancies; and (3) researching its antitumor activity and its clinical pharmacokinetics. The pharmacologic committee of the U.S.S.R. Ministry of Public Health approved the use in Soviet patients of CBDCA, which has been provided to the U.S.S.R. scientists by the NCI. Evaluation of the protocol is underway in the U.S.S.R. as well as in the United States.

From May 23 to June 6, 1982, a medicinal chemist from the University of Michigan was in the U.S.S.R. to participate in a meeting on drug design and bioorganic chemistry as well as to meet with colleagues in a variety of institutes for discussion of drug development and design, advances in bioorganic chemistry, and organic and medicinal chemistry. He returned with abundant information from Soviet colleagues on progress they have made with a number of alkylating anticancer compounds as well as adamantane derivatives, some vinca compounds, and glycopeptide preparations such as the Soviet agent known as kxanerol.

A microbiologist from Pennsylvania State University spent 2 months in the U.S.S.R. pursuing joint experiments on "Herpesvirus Papio: Modulation of Virus Expression in Baboon Lymphoma" at the Institute of Experimental Pathology and Therapy, Sukhumi, Georgian S.S.R. The Sukhumi Center is perhaps the largest facility in the world for primates in captivity. In general, the scientific benefit to American scientists is accessibility to this large colony of baboons and other primates. These animals have been a valuable resource for isolating primate retroviruses, isolating primate herpesviruses and determining their role in the development of certain lymphoproliferative diseases, and identifying genetic factors resulting from inbreeding.



After their participation in the 13th International Cancer Congress in Seattle, Washington, two Soviet chemotherapists spent an additional 3 weeks in the United States visiting centers of excellence related to the studies they are pursuing jointly or independently. Their exchange of information and their interactions with American colleagues related to problems of the biochemical pharmacology of anticancer agents, the design and development of potentially useful anticancer compounds, and the preclinical testing of such agents for their toxicity and efficacy in animal tumor systems.

Meetings of American-Soviet working groups in the program areas of carcinogenesis and cancer prevention will be convened in Moscow in early 1983. Prime consideration will be given to developing work plans for research activities of mutual interest and benefit to cancer patients in both nations.

The spectrum of cooperative cancer research activities, under bilateral agreements between the NCI and cancer institutes of nine nations, is illustrated in Table 4-1.

Table 4-2 indicates that a total of 236 scientists--96 from the United States and 140 from nine foreign nations--participated in collaborative cancer research activities under the aus-

pices of bilateral agreements. More than a third of the total number of scientists spent their sojourns away from home engaging in one-on-one, scientist-to-scientist interactions for collaborative research. Almost a third of the total scientist exchangees pursued activities related to cancer treatment, drug design and development, and preclinical evaluation of potentially useful drugs. Pathology, early detection and diagnosis, biochemistry and molecular biology, and epidemiology followed as scientific areas of high interest and relevance.

### International Cancer Research Data Bank Program

Established by the National Cancer Act of 1971, the International Cancer Research Data Bank (ICRDB) Program has developed into an effective, multifaceted system for the rapid exchange of results from cancer research by the international team of scientists and clinicians. This comprehensive, international resource for cancer information provides a unique service to cancer researchers almost everywhere in the world. To facilitate the transfer of available

Table 4-1.--Cooperative cancer research under bilateral agreements

Cancer research area	F.R.								
	China	Egypt	France	Germany	Hungary	Italy	Japan	Poland	U.S.S.R.
Treatment	E	E	E	N	N	E	E	T	E
Drug development and testing	E		E	N	E	E	E	T	E
Immunology					E		E		
Virology	E		E						E
Genetics									E
Epidemiology	E	E	E		N	E	E	T	E
Control and education									E
Diagnosis and detection	E						E		
Pathomorphology	E	E			E			T	
Autocytology							E		
Carcinogenesis	E		E	E				T	E
Prevention						E			
Biochemistry	E		E				E		
Radiation biology							E	T	E

E = in effect

N = in negotiation

T = information exchanges and training

cancer research data, the ICRDB Program has: (1) established three online computer data bases constituting the CANCERLINE System, which enables scientists to retrieve cancer information easily at more than 3,000 locations within the United States and in 13 other countries; (2) developed a series of publications providing complete coverage of cancer research information, in special formats designed for easy use and quick reference; and (3) supported a variety of specialized information collection, analysis, and dissemination activities.

#### The Computer Databases of the CANCERLINE System

The three data bases constituting the CANCERLINE System are CANCERLIT (cancer literature), CANCERPROJ (cancer research projects), and CLINPROT (clinical protocols).

CANCERLIT contains nearly 325,000 substantive abstracts of information accumulated from published scientific papers and from those presented at meetings, symposia, and conferences; books; technical reports; and research theses. CANCERLIT is growing at an annual rate of nearly 45,000 abstracts, selected from over 2,000 biomedical journals. Because of stringent

input processing requirements and monthly updating of the CANCERLIT data base, the most recently published research results are quickly available to cancer researchers worldwide. Since early 1980, all new literature entries have been indexed with the Medical Subject Heading vocabulary developed by the National Library of Medicine, making retrieval easier during online searching. Ten percent of the accessing of CANCERLIT is conducted by foreign scientists and institutions. Activities related to screening, indexing, and abstracting cancer-related literature are performed for the ICRDB Program under contract.

Descriptions of some 20,000 current cancer research projects in 83 countries are the elements of the CANCERPROJ data base, the most comprehensive source available for ongoing cancer project information. Included in this data base are some 5,000 foreign project descriptions collected by an international network of data input coordinators. Collection, input, and quarterly updating of the project descriptions in CANCERPROJ are performed by a contractor-operated Current Cancer Research Project Analysis Center. The CANCERPROJ connect hours by user type for the first half of FY 1982 were 216.39.

Table 4-2.--The exchange of scientists under NCI's bilateral agreements programs

Collaborating country	Number scientists to . . .		Number scientists from . . .		Area of specialty							
	For meetings	Individual exchanges	For meetings	Individual exchanges	Treatment & Drug Development	Detection & Diagnosis	Carcinogenesis	Biochemistry & Molecular Biology	Nutrition	Prevention	Epidemiology	Pathology
China		7	2	5	3	3		3	1		4	
Egypt				1							1	
France	15	5	3	8	16	1	5	8			1	
Germany (F.R.)	4			2	4	1					1	
Hungary	3	3		5	4	1		3				3
Italy	5	7	20	7	27		1				11	
Japan	37	6	63	13	17	27	10	13		5	9	38
Poland		1		7	2		1	4		1		
U.S.S.R.		3		4	6		1					
Totals	64	32	88	52	79	33	18	31	1	6	27	41



Summaries of nearly 3,500 experimental cancer therapy protocols are the substance of CLINPROT, the data base providing worldwide access to information on new procedures, agents, and combinations of modalities/agents under evaluation for treating cancer patients in major American and foreign cancer centers. Of these protocols, 1,500 are clinically active while the remainder serve as a unique reference source. Collection and input of protocol summaries and quarterly updating of CLINPROT are functions performed by domestic and international contractors. The connect hours for CLINPROT during the first half of FY 1982 were 149.03.

The information contained in the data bases of CANCERLINE is available through the computerized biomedical information network of the National Library of Medicine.

### Special Information Activities of the ICRDB Program

Under contracts with the NCI, three Cancer Information Dissemination and Analysis Centers (CIDAC's) function as information resources in three broad areas of cancer research: the CIDAC for Diagnosis and Therapy, University of Texas System Cancer Center, and M.D. Anderson Hospital and Tumor Institute, Houston; and the CIDAC for Carcinogenesis and for Cancer Virology, Immunology, and Biology, both at the Franklin Research Center, Philadelphia. Each CIDAC is staffed by scientists and served by a consultant network with special expertise appropriate to the fields pertinent to each CIDAC. Within its own subject area, each CIDAC prepares Cancergrams and Oncology Overviews, performs custom CANCERLINE searches, and provides scientific guidance to the ICRDB Program.

The Clearinghouse for Ongoing Research in Cancer Epidemiology is a cooperative project sponsored jointly by the ICRDB Program, IARC in Lyon, France, and the German Cancer Research Center in Heidelberg. The clearinghouse, located in Lyon, collects, processes, and disseminates detailed data on research related to cancer epidemiology and studies of human cancer causation in countries throughout the world. The clearinghouse also prepares lists of epidemiology researchers and resources, responds to technical inquiries, and produces an annual Directory of Ongoing Research in Cancer Epidemiology.

The Latin American Cancer Research Information Project (LACRIP) was developed through the ICRDB Program in collaboration with the PAHO and its Regional Library of Medicine in Sao Paulo, Brazil. LACRIP serves as the source for identifying, collecting, and supplying Latin American biomedical literature, summaries of ongoing cancer-related research projects, and active therapy protocols in Latin America for

inclusion in the CANCERLINE system. PAHO also serves as the center for searching ICRDB data bases and providing documents and data in response to requests for information from cancer researchers in Latin America. In addition, an automatic service that selectively disseminates information to cancer researchers and clinicians in Latin America is provided.

Through LACRIP, a series of collaborative cancer treatment research projects was developed between 10 cancer centers in the United States and 12 cancer centers in Latin America. Although these activities are now supported completely by the NCI Division of Cancer Treatment, LACRIP maintains the clinical data gathered at the Latin American centers. LACRIP also arranges for the exchange of professional staff between the American and the Latin American centers to promote a better understanding of current cancer treatment research and modalities of therapy available in the United States.

In cooperation with the International Union Against Cancer, the ICRDB Program provides partial support for a special Committee for International Collaborative Activities (CICA) within the framework of the union. One of the CICA activities is the collection of data on ongoing cancer research projects, including clinical protocols, from more than 70 countries. CICA personnel identify and promote collaborative projects among cancer centers and cancer scientists in different countries. CICA periodically publishes an updated International Directory of Specialized Cancer Research and Treatment Establishments, which describes more than 700 of the world's cancer centers, their cancer research and treatment activities, and their resources. The International Cancer Patient Data Exchange System (ICPDES) has been established as part of the CICA project. Currently, scientists and clinicians from nine European and five American cancer centers participate in this study, which could result in the development and establishment of the first internationally recognized and standardized tumor registry, from which valuable comparative data would be provided from a multitude of countries on cancer epidemiology, treatment, and prevention.

Entries of cancer case data for six different cancers, from each of the participating centers, is detailed in table 4-3. The entries for each cancer site were accumulated from November 1977 through July 1981.

### Scientist-to-Scientist Communication

The ICRDB Program, through the International Union Against Cancer in Geneva, Switzerland, encourages international scientist-to-scientist communication through the International Cancer Research Technology Transfer Program (ICRETT). The goal of this program is to

Table 4-3.--Patient data, by cancer site and collaborating institute, entered into the ICPDES system

	Breast	Colon	Rectum	Larynx	Hodgkin's	Non-Hodgkin's	Total
M.D. Anderson	3,119	1,055	548	383	384	--	5,489
Mayo	1,370	922	508	201	181	268	3,450
Memorial	947	178	177	70	55	--	1,427
Roswell Park	375	204	106	50	49	38	822
Duke	<u>121</u>	<u>31</u>	<u>30</u>	<u>15</u>	<u>16</u>	<u>1</u>	<u>214</u>
Total U.S.	5,932	2,390	1,369	719	685	307	11,402
Amsterdam	619	28	99	32	57	95	930
Essen	236	12	14	8	36	65	371
Heidelberg	272	61	26	5	36	84	484
Milan	1,474	106	119	184	118	--	2,001
Moscow	818	58	151	126	153	--	1,306
Rotterdam	1,519	74	167	224	110	95	2,189
Bordeaux	1,149	82	159	149	140	49	1,728
Brussels	674	13	73	93	37	13	903
Budapest	<u>1,563</u>	<u>48</u>	<u>98</u>	<u>239</u>	<u>127</u>	<u>5</u>	<u>2,080</u>
Total Europe	8,324	482	906	1,060	814	406	11,992
Total ICPDES	14,256	2,872	2,275	1,779	1,499	713	23,394

promote direct and rapid transfer of information about new or improved technology or methodology between two or more investigators, located in different countries, working on similar research projects. This interaction is accomplished by the support of short-term visits to conduct collaborative research projects in a short time, usually 2 to 4 weeks. Since the inception of the program in 1975, 586 awards had been granted through July 1982.

In many instances, these associations between scientists from different countries developed into significant collaborative studies that otherwise might have lacked the necessary impetus and resources to develop. For instance, a geneticist from the Department of Tumor Biology of the Karolinska Institutet in Stockholm is pursuing molecular analyses of chromosomal translocations in cancer. Through the literature, he learned of a scientist at the Beatson Institute for Cancer Research in Glasgow, Scotland, who has sorted out specific chromosomes and identified their molecular breakpoints. These breakpoints led to chromosome translocations associated with chronic granulocytic leukemia and Burkitt's lymphoma. Newly developed techniques for chromosome sorting by means of the fluorescence activated cell sorter (FACS) were used. Although the Swede had a new FACS available to

him in his own institute, he had had difficulty in applying the instrument for the analyses he wished to perform. During a 3-week exchange, he was able to learn about the features of this unique apparatus and apply FACS techniques for chromosome sorting as well as cloning procedures for small amounts of DNA from translocated chromosomes. Overall, communication between the two scientists supported their collaborative research.

A biochemist from the Institute of Molecular Biology in Salzburg, Austria, spent 1 month in the laboratory of a fellow biochemist at Washington University, St. Louis, Missouri. Both were working on collagenase production in human and animal tumors, recognizing that several human and animal carcinomas contain collagenase and release this enzyme *in vitro*. They perceived, as well, that the role of collagenase in growth and invasiveness of tumor has not been explained precisely. The Austrian was interested in a more sensitive method to detect small amounts of collagenase in the supernatant fluid of tumor cells. He learned of the American biochemist's modification of the enzyme-linked immunosorbent assay, which he believed would meet his own requirements. During his sojourn with the American biochemist, the Austrian scientist was able to master the new technique and return to



his laboratory where he is now studying the de novo synthesis of collagenase, the nature of the latent enzyme, and the source of this enzyme in human skin carcinoma. The successful collaborative efforts of the two biochemists continue.

A biochemical pathologist from the Yale University School of Medicine had been studying the phenomenon of epidermal (epithelial) cell movement, which is relevant to the histologic and pathologic process of wound closure and epithelial cancer cell invasion and metastasis. In analyzing these processes, he isolated a molecule from serum that epithelial cells need in order to move in vitro. This molecule, a glycoprotein named epibolin, is necessary and sufficient for epidermal cell movement. In the absence of serum, no epidermal cell spreading is observed, and in the presence of epibolin-antibody, serum does not support epidermal cell spreading. The purpose of his visit with a colleague at the University of Zurich was to learn what specific role the spreading protein plays in the movement of cancer cells, since cancer cell motility is central to the problem of neoplastic invasion and metastasis. The Swiss scientist, a world-renowned scholar of cancer cell movement, developed unique methods for measuring cancer cell motility. In addition, he developed several squamous cell carcinoma lines for such studies. By virtue of his experience in Switzerland, the American scientist was able to confirm his hypothesis and his experiments are consonant with the conclusion that the glycoprotein epibolin is the necessary component for in vitro spreading of cells from human squamous carcinoma.

A radiotherapist/epidemiologist from the John F. Kennedy Memorial Hospital in Monrovia, Liberia, journeyed to the NCI of Canada, in Toronto, where he spent 1 month designing, constructing, administering, and analyzing questionnaires for case-control and cohort studies used in epidemiology. After learning about questionnaire design, questionnaire methods, and indepth interviewing, he attended field studies with several Canadian interviewers to gain practical insight into problems associated with interviewing. He learned the procedures for choosing controls for the various types of case-control and cohort studies as well as the validation and sensitivity of testing and final evaluation of data. At the end of his stay, he was able to put together the skeleton of a questionnaire for a case-control study scheduled for completion in Liberia and tried out first in a pilot study and later as a multicenter study in collaboration with his colleagues in Africa.

A surgeon from the Yale University School of Medicine pursued intense study for 3 weeks with a surgeon from the University Hospital in Zurich, from whom he obtained instruction in both surgical anatomy of the cranial base and the actual operative technique for treatment of tumors located at the skull base. The principal deter-

minant of patient survival in the treatment of tumors in this anatomical site involves the ability to obtain total gross tumor removal before instituting adjuvant radio- or chemotherapy. Through actual observation of surgical procedures, video tapes, and the use of the Swiss surgeon's extensive library, the American surgeon obtained a good deal of firsthand, practical information. This experience enabled him to perform the Swiss procedure at Yale.

A photochemist from the Agricultural Research Organization in Bet Dagn, Israel, spent 1 month in the Laboratory of Pathophysiology of the NCI. He wanted to understand the initial chemical events that follow photoexcitation of the porphyrin molecule and its subsequent interaction with other cell constituents. He was interested in optimizing data for the preferential uptake and retention by malignant tumors of porphyrins, which are photochemically active compounds. Because porphyrins are efficient photodynamic sensitizers and certain malignant cells become fully vulnerable to light, he hoped to learn the mechanism(s) by which tumor cells are inactivated during exposure to porphyrin and irradiation.

An English biochemist/physician spent 2 weeks in the Cancer Treatment and Research Center in San Antonio, Texas, to study the techniques currently used to grow colonies of human tumor cells on soft agar. The visit and exchanges enabled him to make small but important modifications to the techniques currently used in his laboratory for the culture of ovarian, breast, and colonic carcinoma. As well, he was able to compare the up-to-date results obtained from cytotoxic drug assays in this laboratory using reduction in colony-forming activity as an end point. Since his return to South Hampton, England, he has been able to redefine the objectives of his present project towards: (1) using an animal model to see if the in vitro assay can be truly predictive of in vivo activity of cytotoxic drugs; and (2) looking more closely at the biology of colony formation by tumors and to improve the proportion of growing in vitro.

In summary, table 4-4 designates the disciplinary studies pursued by the 586 ICRETT awardees, while table 4-5 indicates the international flavor of the ICRETT Program and the interaction between scientists from 47 countries/areas.

### NIH Visiting Program

During 1982, scientists of the NCI received 260 Visiting Scientists, Associates, and Fellows from 45 countries who came to the United States to engage in collaborative cancer research activities. Five of the visitors were appointed as Experts and 68 came as Guest Workers, whose financial support was provided by sources other

Table 4-4.--International cancer research technology transfer

Disciplines	1976 6 months	1977	1978	1979	1980 + JFM 81	1981 Apr 81- Mar 82	1982 April/ June	Total
Epidemiology, biostatistics, and registries	--	3	5	7	7	5	2	29
Biochemistry, molecular biology, and biophysics	5	14	14	11	11	7	2	64
Viral carcinogenesis	7	13	10	9	11	6	1	57
Chemical carcinogenesis	3	14	8	13	12	5	1	56
Cell biology and cell genetics	1	15	11	8	19	14	2	70
Experimental pathology (including histopathology and cytology)	4	5	12	14	10	3	1	49
Immunology	5	19	25	31	33	11	--	124
Experimental chemotherapy	6	3	2	9	2	2	--	24
Surgery	--	1	2	--	4	--	1	8
Clinical chemotherapy and endocrinology	2	3	1	8	7	3	--	24
Radiobiology and radiotherapy	5	4	7	10	9	7	1	43
Controlled therapeutic trials	1	--	1	4	--	--	--	6
Detection and diagnosis	1	6	4	1	8	1	--	21
Behavioral and social sciences and the relationship to cancer	--	--	1	--	4	1	--	6
Environmental factors and prevention	--	2	--	1	2	--	--	5
Totals	40	102	103	126	139	65	11	586

than the NCI. These visiting scientists pursued their research in the laboratories of the NCI Divisions of Cancer Treatment, Cancer Cause and Prevention, and Cancer Biology and Diagnosis. These mutually beneficial associations afforded the NCI host scientists opportunities to learn from their visitors about cancer problems in a given foreign country; about factors peculiar to that nation that might be related to the morbidity and mortality of cancer; and about activities underway toward the management, treatment, and prevention of cancer. Reciprocally, the foreign visitors enjoyed unique opportunities to improve their mastery of the scientific method or to develop their potential for significant contributions to basic and/or clinical research. The value of this scientific interaction is indis-

putable because cancer patients throughout the world are benefiting from improved care.

#### Extramural Programs

During 1982, the Divisions of Cancer Treatment (DCT) and Cancer Cause and Prevention (DCCP) maintained extensions of their programmatic objectives in foreign countries through 18 contract research activities, compared to 34 during the previous year and 53 during 1980. No contractual research was in effect to extend the research effort of the Division of Cancer Biology and Diagnosis (DCBD).

The Division of Extramural Activities (DEA) provided the fiscal support, through 59 grants, to



scientists in foreign institutions conducting basic and applied cancer research.

Institutions in 17 nations were recipients of NCI grants and contracts. Thus, the outreach of NCI support extended to Australia, Belgium, Canada, Denmark, Finland, France, Ghana, Israel, Italy, Japan, Korea, South Africa, Sweden, Switzerland, Tanzania, Tunisia, and the United Kingdom.

#### Division of Cancer Treatment

DCT research contracts have been awarded to investigators in nine institutions of five foreign countries for studies related to the characterization of anticancer agents, the search for potentially useful anticancer agents such as those of microbial and natural origin, the screening and testing of such compounds, their biochemical pharmacology and toxicology, the synthesis of radiation sensitizing agents, and clinical trials on specific cancers. One contract is specifically for the production and delivery of human lymphoblast interferon. Examples follow of this international collaborative effort in cancer drug design and development and in preclinical and clinical evaluation.

Through its Cancer Chemotherapy Research Collaborative Office at the Institut Jules Bordet in Brussels, Belgium, the DCT maintains interaction with investigators of European nations concerning ongoing cancer research programs on both continents. The Brussels office has been especially useful in disseminating information on experimental and clinical pharmacology and clinical trials and organizing symposia conducted jointly by American and European investigators. The Institut Jules Bordet provides a flow of new agents with potential anticancer activity to the European pharmaceutical industry.

Under contract, materials collected in northern Europe are screened against animal tumors at the Institut Jules Bordet in accordance with established *in vivo* protocols. Approximately 11,000 substances that have been identified as potentially useful anticancer agents are currently being tested.

Under contract to the NCI, the Institute of Cancer Research in England is conducting research on design, synthesis, and evaluation of novel compounds, both nitroimidazoles and other heterocycles, as potential radiation sensitizers. Several classes of heterocycles have been synthesized and are in the process of evaluation. Other activities in the Institute of Cancer Research involve: (1) validation of human tumor xenografts as models for cancer chemotherapy; (2) the use of human tumor xenografts and transplantable mouse tumors for testing new compounds of interest to the NCI; (3) the toxicology, pharmacology, and initial clinical trials of new drugs developed in this project; and (4) studies of the biochemical basis for treatment

Table 4-5.--Countries/areas of origin of ICRETT awardees and their destinations, 1976-82

Origin		Destination	
Argentina	15	Argentina	1
Australia	4	Australia	10
Austria	6	Austria	1
Belgium	9	Belgium	6
Brazil	6	Canada	12
Bulgaria	3	P.R.C.	8
Canada	15	Taiwan	1
P.R.C.	7	Colombia	1
Taiwan	2	Denmark	5
Colombia	1	Finland	7
Czechoslovakia	3	France	35
Denmark	1	Germany (F.R.)	35
Egypt	1	Hungary	2
Finland	5	Iceland	1
France	37	India	2
Germany (F.R.)	27	Israel	8
Greece	4	Italy	10
Hungary	4	Japan	24
India	18	Malaysia	1
Iran	2	Mexico	1
Israel	46	Netherlands	11
Italy	42	New Zealand	3
Japan	15	Norway	4
Kenya	1	Peru	1
Liberia	2	Poland	1
Malaysia	2	Sweden	34
Mexico	3	Switzerland	29
Netherlands	11	United Kingdom	69
New Zealand	2	U.S.A.	258
Nigeria	8	U.S.S.R.	3
Norway	12	Venezuela	2
Peru	1		
Philippines	1		
Poland	11	31 countries/areas	586
South Africa	1		
Spain	4		
Sri Lanka	2		
Sweden	24		
Switzerland	5		
Thailand	3		
Turkey	1		
Uganda	1		
United Kingdom	74		
Uruguay	2		
U.S.A.	135		
Yugoslavia	6		
Zambia	1		
47 countries/areas		586	

Table 4-6.--The NCI-PAHO collaborative cancer treatment research program  
by number of protocols and patient accrual

Latin American Center	Protocols	USA Cancer Center	Patient accrual
Grupo Argentino de Tratamiento de los Tumores Solidos (GATTS) Buenos Aires, ARGENTINA	2	Georgetown University Washington, D.C	168
Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) Buenos Aires, ARGENTINA	5	Georgetown University Washington, D.C.	341
Instituto Angel H. Roffo Buenos Aires, ARGENTINA	2	Georgetown University Washington, D.C.	15
Instituto Nacional de Cancer Rio de Janeiro, BRAZIL	1	M.D. Anderson Hospital and Tumor Institute Houston, TEXAS	137
Fundacao A.C. Camargo Sao Paulo, BRAZIL	1	Memorial Sloan-Kettering Cancer Center New York, NEW YORK	45
Universidad Catolica de Chile Santiago, CHILE	2	Wisconsin Clinical Cancer Center Madison, WISCONSIN	274
Instituto Nacional de Cancerologia Bogota, COLOMBIA	1	Roswell Park Memorial Institute Buffalo, NEW YORK	98
Hospital de Ninos "Dr. C.S. Herrera" San Jose, COSTA RICA	NA	Baylor University Medical Center Dallas, TEXAS	(NA)
Hospital San Juan de Dios San Jose, COSTA RICA	NA	Baylor University Medical Center Dallas, TEXAS	(NA)
Hospital de Oncologia Mexico City, MEXICO	1	New York University Cancer Center New York, NEW YORK	45
Instituto Nacional de Enfermedades Neoplasicas Lima, PERU	8	Comprehensive Cancer Center for the State of Florida Miami, FLORIDA	608
Hospital de Clinicas "Dr. Manuel Quintela" Montevideo, URUGUAY	3	University of Maryland Cancer Center Baltimore, MARYLAND	109
Instituto de Oncologia "Luis Razetti" Caracas, VENEZUELA	NA	Yale University Medical Center New Haven, CONNECTICUT	(NA)
13 centers/9 countries	26	10 centers	1840

NA = newly admitted to CCTRP.



response or failure aimed at the design, synthesis, and detailed evaluation of new drugs.

Under contract, the NCI maintains a Chemotherapy Liaison Office in the Japanese Foundation for Cancer Research in Tokyo. The program is designed to foster close collaboration between American and Japanese investigators in the development and application of new clinical anticancer drugs and in the exchange of pre-clinical experimental and clinical scientific knowledge and materials requisite for maximum progress in cancer therapy.

Scientists at the Mario Negri Institute of Pharmacologic Research in Milan, Italy, aid the NCI, under contract, with a multidisciplinary approach to drug development. The research tasks include: (1) collection and screening of antineoplastic agents obtained from southern Europe; (2) screening of immunochemotherapeutic agents; and (3) pharmacologic studies of new agents with emphasis on the relationship of pharmacokinetics with *in vivo* antitumor effects.

In association with the Muhimbili Medical Center in Tanzania, the DCT is engaged in a study of the use of oral 13-cis retinoic acid as a chemopreventive agent of skin cancer in albino Africans. These people, living in the equatorial zone, are subject to the most intense ultraviolet radiation on the surface of the earth and therefore to a 100 percent greater probability of skin cancer.

Five years ago, through the ICRDB Program's special information activity, LACRIP, collaborative clinical studies were developed among nine cancer centers in the United States and six centers in Latin America. This cooperative relationship with Latin American cancer institutes is now managed by the DCT as the NCI-PAHO Collaborative Cancer Treatment Research Program. Currently, investigators in 13 Latin American cancer institutes/hospitals and in 10 American cancer centers are pursuing joint research activities. The treatment protocols now in evaluation include therapeutic concepts in hematologic malignancies, childhood malignancies, breast cancer, gynecologic cancer, gastrointestinal cancer, and osteosarcomas. Multimodal concepts in solid tumors are being pursued in advanced breast and head and neck cancer. Over the total life of the program as many as 37 therapy protocols have been active in a given year. Eleven of these protocols have been completed or terminated, leaving 26 still under active investigation. Since the inception of this multinational effort, 2,342 patients have been accrued under the various protocols. The collaborating cancer centers, the numbers of active protocols, and patient accrual are listed in table 4-6. Table 4-7 indicates the cancers being studied in various organ sites.

Personnel of the DCT play key roles in the NCI bilateral agreements with China, Egypt, France, the Federal Republic of Germany, Italy,

Japan, and the U.S.S.R. through participation in clinical trials, preclinical screening and testing of potentially useful anticancer agents, evaluation of the activity of substances indicating properties for biologic response modification, and programs in experimental/development therapeutics.

#### Division of Cancer Cause and Prevention

The DCCP maintains active associations with international organizations and agencies that have well-defined objectives in cancer research, especially its cause and prevention. The DCCP is also engaged in collaborative contract research in seven institutions or agencies in six foreign nations. These foreign extensions of the DCCP research program enable the Division to support fundamental studies on normal and malignant cells in relation to such carcinogens as viruses and chemicals, as well as epidemiologic studies of human populations for the identification of risk factors predisposing individuals to various cancers. Excellent model systems are available to scientists studying the effects of potentially carcinogenic factors in the environment. Thus, studies are related primarily to three major program areas within the DCCP: biologic carcinogenesis, chemical/physical carcinogenesis, and epidemiology.

The binational programs on which the DCCP collaborates provide significant epidemiologic opportunities for cancer research. This year, joint studies and exchange programs enabled scientists of the Cancer Institute Hospital in Beijing to pursue clues drawn from the recent county-based maps in China and to study the changing risks among Chinese migrants to the United States. Reports were prepared on the geographic correlations within China between cancers of the cervix and penis and colorectal cancer and schistosomiasis and on the patterns of childhood cancer in Chinese populations around the world. Collaborative analytic investigations on cancers of the esophagus and lung, trophoblastic neoplasms, and T cell leukemia are also being developed.

Through a contract with the DCCP, scientists at the Chaim-Sheba Medical Center in Israel are determining the incidence of cancer in 10,000 Israeli children irradiated for ringworm of the scalp, in 10,000 nonexposed persons selected from the general population, and in 5,000 non-exposed siblings. This effort is of significance in the study of patients irradiated for benign diseases because it allows an evaluation of biologic mechanisms for carcinogenesis in humans. The minimal confounding effects of carcinogenic influences, and the possibly greater susceptibility of young people to environmental carcinogens, improve the chances of detecting radiogenic effects and provide an opportunity for lifetime studies of cancer incidence.

Table 4-7.--NCI-PAHO collaborative cancer treatment research program by location and number of active protocols

PAHO nation and center		Active protocols									Total
		Breast	Head and neck	Lung	Brain tumors	Medulloblastoma	Myeloma	Sarcomas	Gastrointestinal	Lymphoma- Leukemia	
Argentina	GATTS <sup>a</sup>						1	1			2
	GATLA <sup>b</sup>				1	1	1		2		5
	ROFFO		1							1	2
Brazil	Rio de Janeiro		1								1
	Sao Paulo		1								1
Chile		1						1			2
Colombia									1		1
Mexico										1	1
Peru		3	1				1	1		2	8
Uruguay			1	1		1					3
Total		4	5	1	1	1	3	3	3	4	26

<sup>a</sup> Grupo Argentino de Tratamiento de los Tumores Solidos - Hospital Militar Central

<sup>b</sup> Grupo Argentino de Tratamiento de la Leucemia Aguda

#### Division of Extramural Activities

Grants by the DEA have been made available to institutions and organizations in 11 foreign countries. The scientific investigations under the 59 DEA grants include both basic and applied research and range across the spectrum of the thrusts and objectives of the NCI. Among these are the National Research Council of Canada's assays for and studies of the action of carcinogens and "promoters" of carcinogenesis. Other studies being pursued in Canadian universities and institutions include the pathogenesis of liver cancer induced by chemicals, the role of anti-tumor action of nitrosoureas, DNA repair/replication in chemical carcinogenesis, the metabolism and carcinogenicity of haloaromatic pollutants, and melphalan interaction with amino acids in human cells. At the University of Lon-

don a study is underway on the metabolic activation of the polycyclic hydrocarbons as well as a study of the therapeutic response of human tumor xenografts. In Finland, at the University of Helsinki, investigations are being pursued of natural and tissue-specific immunity to human neoplasms and fibronectin and its loss in malignant transformation. Scientists at the Weizmann Institute of Science in Israel are studying the control of gene expression in tumor viruses and in cells. At that institution, as well, studies are underway of receptors and growth factors for neoplastic cells and the modulation of cellular responses by membrane fluidity.

These research grant activities provide the NCI with opportunities to associate with and take advantage of the foreign expertise available in basic and clinical research that is directly relevant to the thrusts and goals of the NCI.



## Chapter V

# National Heart, Lung, and Blood Institute

### Introduction

The United States plays an important role in international efforts to control heart, lung, and blood diseases. This role has evolved through the contributions of the U.S. scientific community, in concert with the U.S. national programs initiated under the 1972 mandate from the President and the Congress. The mandate, while significantly broadening the scope and depth of the programs of the National Heart, Lung, and Blood Institute (NHLBI), also created new opportunities for U.S. scientists to collaborate with scientists engaged in similar efforts in other countries. The concerted government and private sector efforts implemented in the United States in recent years have resulted in significant improvements in the health of the U.S. population. While mortality rates for coronary heart disease are increasing in many countries, they have been declining in the United States. In recognition of this success, the international medical research community hopes to learn important lessons from the U.S. national programs. Thus, scientists and administrators in other countries frequently look to the United States for expertise in research methodology, design strategies, and implementation of research findings at the community level. Conversely, through the Institute's international programs, U.S. scientists are able to carry out comparative studies and analyses not possible through national efforts alone. A number of bilateral agreements have been drawn up that combine U.S. resources with those from other countries on a cost-sharing basis.

The broad goals of the NHLBI international programs are

- To develop international programs relevant to the goals and priorities of the U.S. national programs in heart, lung, and blood diseases and blood resources; and
- To develop international contacts, activities, and programs of mutual interest and benefit to the United States and to the cooperating country or countries in areas related to the Institute's national mission.

The NHLBI international programs emphasize basic research to enhance data generated in

domestic studies, clinical investigations, design and implementation of epidemiological studies, and programs in prevention, education, and control. By combining international resources with national resources, scientists can use scarce research funds more effectively in the United States as well as in the collaborating countries. Joint studies by U.S. and foreign scientists with complementary skills, approaches, or resources accelerate scientific research by consolidating the management of the research problem, ensuring comparability of data, and generally improving the analysis of data.

NHLBI international programs have impacts on health problems in the United States and abroad. A growing network of countries is interested in studies similar to those implemented by the NHLBI. The Lipid Research Clinics studies are an example of the strong international effort in arteriosclerosis. Under NHLBI sponsorship, epidemiological data have been collected since 1972-73 on populations in the United States, Canada, Israel, and the U.S.S.R. Analyses of the data and publications of the results are continuing. These studies compare lifestyles to genetic determinants of cardiovascular disease, with specific emphasis on the prevalence of lipid disorders in different populations. Perhaps the most important contribution of these studies is the international standardization of data collection and analyses. These procedures are also being used to organize similar studies in China and Poland so that future comparisons between the United States and these two countries will be possible as well. In a similar study sponsored by PAHO, clinics in Mexico, Brazil, and Jamaica will be standardized to generate comparable data on nutrition and cardiovascular diseases in Latin America and Caribbean populations.

Broad international interest in hypertension has also been generated. The success of the Institute's National High Blood Pressure Education Program (NHBEP) and the Hypertension Detection and Followup Program (HDFP) has contributed to this interest. For instance, the Federal Republic of Germany is using these programs as models for its High Blood Pressure Education Program initiated in 1980. Activities planned under the U.S.-Kuwait Technical Cooperation Program in Health also build on the experiences gained in the NHBEP and HDFP.

Studies of hypertension are important components of the bilateral programs with China, Japan, and the U.S.S.R. Each of these bilateral programs provides unique opportunities for expanding the knowledge base gained from U.S. national data. In the case of the U.S.-U.S.S.R. program in hypertension, the joint studies emphasize biobehavioral research. The U.S.-Japan studies focus on the role of nutrition, while the U.S.-P.R.C. cooperation explores the factors that may be responsible for the observed differences in rates of hypertension in north and south China.

The above examples show how studies initiated by NHLBI have generated interest in other countries and international organizations in testing similar hypotheses in a multinational context. The insights resulting from these analyses can lead to a broader understanding of the relative importance of diet, heredity, lifestyle, and environment in the etiology of cardiovascular disease. These studies may also lead to new approaches to the treatment and prevention of cardiovascular disease.

Although NHLBI international activities in basic research are conducted on a relatively small scale, results can have important implications for the broader scientific community. Research results from U.S. cooperation with Italy, France, Japan, the Federal Republic of Germany, and the U.S.S.R. are described in this report.

One important impact of the NHLBI international programs has been on the scientific literature. Under the bilateral programs, U.S. scientists and foreign experts have collaborated on many scientific publications, proceedings, and books, making the information available to the scientific community at large. These publications report on the results of joint planning of research, joint implementation, and joint analyses of data in a manner not possible through national approaches alone. A number of proceedings of U.S.-U.S.S.R. joint symposia were published in FY 1982. Several books, reporting on the results of U.S.-Italy joint cooperation, have been published by Raven Press and Karger Verlag. The proceedings of a U.S.-Poland joint symposium on cardiovascular disease have also been published. The first papers from the U.S.-P.R.C. studies are being prepared for publication.

## Summary of International Programs and Activities

The Institute's international programs and activities are carried out within the Institute's mandates under the National Heart, Lung, and Blood Program. The following sections summarize NHLBI cooperative activities with other countries during FY 1982.

## Bilateral Agreements and Other Country-to-Country Activities

### Canada

Cardiovascular disease is the leading cause of death in Canada, as in the United States. Mortality from this disease has been declining in both countries, although more rapidly in the United States than in Canada. U.S.-Canadian cooperation in areas related to NHLBI's mission has been longstanding. Many NHLBI-sponsored clinical trials have a Canadian component. In FY 1982, Canadian investigators participated in the following studies:

- **The Beta Blocker Heart Attack Trial:** A trial, completed in October 1981, that demonstrated the effectiveness of the drug propranolol in reducing mortality among heart attack victims;
- **Coronary Artery Surgery Study:** A study to evaluate the efficacy of coronary artery bypass surgery in reducing morbidity and mortality from heart disease;
- **Lipid Research Clinics Program:** An international network of clinics conducting the Coronary Prevention Trial to test the hypothesis that reduction of serum cholesterol in men with elevated cholesterol will reduce coronary heart disease;
- **Multiple Risk Factor Intervention Trial:** A prevention program to investigate whether modification of three cardiovascular disease risk factors--smoking, high blood pressure, and elevated serum cholesterol--will reduce the incidence of myocardial infarction and death from coronary heart disease;
- **Clinical Study of Intermittent Positive Pressure Breathing:** A trial to evaluate the effects of this treatment when used as an adjunct to the care of ambulatory patients with chronic obstructive lung disease;
- **Prevention of Neonatal Respiratory Distress Syndrome with Antenatal Steroid Administration:** A trial to determine whether antenatal administration of steroids can reduce the incidence, morbidity, and mortality from this condition among infants at risk.

### China

An agreement between the Government of the United States and the Government of the People's Republic of China on Cooperation in Science and Technology was signed in January 1979. The subsequent U.S.-P.R.C. Protocol for Coop-



eration in Science and Technology of Medicine and Public Health, signed in June 1979, identified cardiovascular disease as one of the seven areas of initial cooperation.

At the U.S.-P.R.C. Second Joint Science and Technology Commission Meeting in October 1981, the U.S. cochairman noted that the cooperative program ranked with those of highest priority to the United States and that the joint activities were now yielding mutually beneficial results. One such activity has been the development of a joint protocol for collaborative research on the epidemiology of cardiovascular disease and its risk factors. The protocol defines a study of urban and rural populations (men and women) in north and south China. After completion of a pilot study in the spring of 1982, the U.S. working group visited China in the fall of that year to initiate the laboratory standardization program, train staff, prepare study forms, and discuss data processing and methodology of the biochemical measurements.

During FY 1982, a number of Chinese delegations visited the NHLBI. In May 1982, a P.R.C. study group on advances in research on atherosclerosis met with Institute staff to discuss current research in atherogenesis, hypertension, nutrition and cardiovascular disease, pathology, and the Lipid Research Clinics Program. Later that month the director of the new Beijing Heart, Lung, and Blood Vessel Medical Center and a member of his staff visited the NHLBI. Two Chinese specialists in lung diseases held in-depth discussions with the staff of the NHLBI's pulmonary laboratories. In March, two Chinese fellows completed a year of joint research in the United States. The first of these worked on the biochemistry of atherosclerosis and prepared two papers for publication in American journals. The topics are the quantitation of apolipoprotein H in patients with dyslipoproteinemia and the quantitation and distribution of apo A-4 in familial dyslipoproteinemia. The second scientist performed cellular studies of human atherosclerosis at the University of Washington in Seattle.

Two Chinese fellows performed research in the NHLBI's Pulmonary Branch with support from WHO. The first of these scientists worked on defining the role of the eosinophil in inflammatory lung disease and developed an animal model useful for studying these diseases. She presented her work at the American Thoracic Society Meeting in May and an abstract was published in the proceedings. The second scientist worked on elucidating the pathogenesis of fibrotic lung disease, one of the principal lung diseases in China.

#### Egypt

Discussions of potential exchange activities with Egypt continued during FY 1982. A number

of proposals from Egypt have been received in recent years, primarily in hypertension and rheumatic heart disease. Informal exchanges of experts are underway in hypertension. Two visits by Egyptian physicians took place in FY 1982. Both experts were interested in the Institute's programs in the cardiovascular area and in the potential for future cooperation.

#### Finland

U.S. representatives reviewed a draft U.S.-Finland Agreement for Health Cooperation designed to strengthen existing links between the scientific communities of the two countries and to promote cooperation in health care and biomedical research. Future collaboration will include exchanges of specialists and information, organization of conferences and lectures, and development of joint studies. During a visit to the NHLBI by the Secretary General, Ministry of Social Affairs and Health of Finland, in October 1981 the potential of future exchanges in the cardiovascular area was discussed. Because Finland and the United States are among the countries with the highest rates of heart disease in the world, both countries are emphasizing prevention programs to deal with the problem, and, in fact, informal exchanges of specialists are underway.

#### France

The pathology of interstitial lung diseases has been the focus of a number of joint studies under the agreement between the NHLBI and INSERM. This agreement was originally signed in 1970, and in 1980 a 3-year project on interstitial lung diseases was initiated between the NHLBI and INSERM.

During FY 1982, two studies were completed and the results submitted for publication: one on histiocytic disorders and the other on hypersensitivity pneumonitis. The first study was based on the joint experiences of two French teams and one American team. The second study of the histological and ultrastructural features of hypersensitivity pneumonitis was based on the findings of pooled lung biopsies obtained from 18 patients. A French scientist visited the United States twice for joint experiments. She participated in immunofluorescence studies of the skin lesions in sarcoidosis, using monoclonal antibodies. Upon her return to France, she applied the techniques to cells collected by bronchoalveolar lavage as well as to samples obtained surgically by open lung biopsies. Two reports are being prepared for publication. Two U.S. scientists made followup visits to Paris to continue cooperative studies.

During FY 1982, the NIH-CNRS program supported a joint study to determine the role of the natriuretic factor in the initiation and/or main-



tenance of essential hypertension in humans. The natriuretic factor is a substance in the blood that causes excretion of abnormal amounts of sodium in the urine. Its structure, function, site of formation, and factors causing its release into the circulation are unknown. Direct and indirect evidence suggests that sodium efflux from white blood cells can be inhibited by the plasma of hypertensive subjects but not by the plasma of normotensive subjects. To confirm these observations, U.S. and French scientists are isolating the natriuretic factor using new chemical isolation techniques and bioassay procedures. During the course of this joint work plasma fractions from hypertensive and normotensive patients were analyzed. One fraction was found that markedly inhibited the enzyme Na-K ATPase. Further isolation and purification of the natriuretic factor is planned in order to produce monoclonal antibodies that will then be used to quantitate the factor in individual plasma samples. This work will continue in France. Once sufficient quantities of the natriuretic factor are prepared, the U.S. laboratory will examine possible physiologic roles for the substance and will hope to offer new insights into its role in the etiology of essential hypertension.

#### Federal Republic of Germany

Cooperative activities in cardiovascular research are conducted under a joint U.S.-FRG agreement between the Department of Health and Human Services and the Federal Ministry for Research and Technology of the Federal Republic of Germany, signed in 1976 and extended for 5 years in 1981. The emphasis is on linking ongoing projects in arteriosclerosis and hypertension.

During joint scientific and health policy discussions held in the FRG in 1981, the following cooperative activities were agreed upon for the next 2 years:

- Internationally comparable surveillance and monitoring of cardiovascular morbidity and mortality and their association with risk factors and health practices;
- Development and exchange of techniques and strategies for intervention studies; and
- Development and exchange of techniques for evaluation and validation of approaches to intervention.

Since 1981, U.S. investigators have collaborated with German scientists in the design and planning of a Multicenter Intervention Trial (MIT) and the German National Health Survey, which will provide the necessary background information for the MIT. The German MIT is an 8-year project. A 5-year trial will be preceded

by 2 years of pilot studies and followed by 1 year of data analysis. To ensure that internationally comparable data are obtained, U.S. and FRG investigators have agreed to collaborate closely throughout the studies.

Early in FY 1982, a German delegation visited the NHLBI, the Central Patient Registry and Coordinating Center for the Lipid Research Clinics Program, and the National Center for Health Statistics. A joint working meeting focusing on the German NHS and the MIT was held at the NHLBI for a review of the protocols for these activities. An in-depth joint analysis was performed with special emphasis on standardizing methods and procedures in the following areas: laboratory procedures; electrocardiography; health behavior assessment including nutritional aspects and use of health services; assessment of psychological factors; evaluation of endpoints; and organization, management, and data handling.

A second German delegation visited the NHLBI to develop the syllabus for an advanced 2-week workshop in epidemiology funded by the German Government. This workshop, to be held in Germany in the fall of 1983, will be taught by a combined U.S.-FRG faculty. The purpose of this workshop is to develop the necessary epidemiological skills so that members of the MIT staff can produce internationally comparable surveillance and monitoring data. Also, late in FY 1982, an FRG delegation visited several community-based intervention projects in the United States to develop and exchange strategies for intervention studies and validate their proposed approaches to intervention.

Because hypertension is a serious health problem in the FRG, as in the United States, the German Government is taking steps to bring it under control. Several exchanges have taken place in this area. Because of the success of the American HDFP, the Germans have initiated a National High Blood Pressure Education Program modeled on the U.S. program. In this way, they hope to duplicate some of the declines in cardiovascular disease experienced in the United States in recent years. A German scientist worked for a year with Hypertension Detection and Followup Program staff in the United States to develop the methodology for a pilot study for the German equivalent. This cross-sectional study, completed in FY 1982, was carried out on men and women 30-69 years of age, drawn from selected census tracts in Munich. Of the 3,198 persons selected for the pilot study, 2,216 individuals or 70 percent took part. One of every three participants was found to be hypertensive and nearly half the hypertensives (45.8 percent) did not know of their disease. Of those who knew, only half were under treatment and of these only one-third had their condition effectively controlled. In summary, only 11.2 percent of the hypertensive patients in the FRG pilot



study had their high blood pressure effectively controlled at the onset of the program. The study results illustrate the seriousness of the problem and the feasibility of gathering internationally comparable epidemiological data. The planned approach is envisioned as a multicenter, cooperative, FRG-wide effort aimed at detecting and treating all Germans who have hypertension. Several basic research projects in the area of hypertension are also being carried out by individual U.S. and German investigators cooperating informally.

The FRG Minister of Youth, Family, and Health, who visited the NHLBI to discuss ongoing cooperative studies with NHLBI staff, showed particular interest in Institute programs to control hypertension.

### Hungary

An Umbrella Agreement between the Hungarian People's Republic and the Government of the United States on Cooperation in Culture, Education, Science, and Technology was signed in October 1979. The agreement calls for exchange and cooperation in areas of mutual benefit and common interest.

Contacts between the United States and Hungary continued during FY 1982. In July 1982, a Summary of Discussion was signed for exchanges of scientists in the cardiovascular area. Topics include prevention and control of coronary heart disease and hypertension, cardiac surgery, diabetes and heart disease, peripheral vascular disease, noninvasive and invasive assessment of left ventricular function, and pharmacodynamic and pharmacokinetic studies with cardiovascular drugs. Both sides agreed to exchange up to two scientists each year for a total of 4 months.

### India

The Director-General of the Indian Council of Medical Research requested information from the NHLBI on the Institute's strategic plan for research in cardiovascular disease with a view toward implementing a similar plan. The U.S.-India Subcommission on Science and Technology and Working Group on Medical and Health Sciences met in December 1981 to discuss potential areas of cooperation. A new initiative in scientific and technological cooperation with India was identified in July 1982. The details of the initiative will be worked out by a Blue Ribbon Panel composed of eminent U.S. and Indian experts. The NHLBI has proposed that consideration be given to rheumatic fever and rheumatic heart disease in children, since the incidence of these diseases is increasing rapidly in India. The diseases, associated with high morbidity and mortality, incur high medical costs.

### Israel

The population of Israel offers unique opportunities for epidemiologic research. The diverse ethnic and cultural backgrounds of the Jews who migrated there from many countries provide important clues to the relative roles of genetics and lifestyle in the etiology of cardiovascular disease. The NHLBI has funded collaborative research with Israel through grants and contracts for over a decade. In January 1980, a 5-year agreement for cooperation in health was signed by the U.S. Department of Health and Human Services and the Israeli Ministry of Health, and efforts are underway to identify additional opportunities for cooperative activities.

In 1975, the NHLBI established the Jerusalem Lipid Research Clinic to study the prevalence of hyperlipoproteinemia among 17-year-old army inductees and a subsample of their fathers. This clinic, part of the international Lipid Research Clinic Program, adheres to highly standardized methods of data collection and analysis. The Jerusalem population represents 55 countries of origin and is divided into four broad groups: Israeli, Asian, North African, and European/American. Subject screening was completed in 1980.

Preliminary results show important differences in blood lipid profiles, which can be correlated with the country of paternal origin. Total cholesterol levels were lowest in teenagers of North African descent, highest in youths of European and Israeli origin, and intermediate in those from Asia. Triglyceride levels were lowest among North Africans, but Asian and Israeli groups had higher values than the Europeans. Mean plasma high density lipoprotein cholesterol levels were highest among youths with fathers of European and American origin and lowest in those of Asian and North African descent. Second generation Israelis ranked intermediate between the two groups. Thus, patterns of lipid and lipoprotein levels previously observed in adult immigrants persist into a generation of native-born Israelis. These results were consistent with the observed differences in the dietary intake of total fat, saturated fat, and cholesterol. The highest intake of these nutrients was found in children of native Israeli or European/American fathers. Comparison of the Israeli diet with that of a group from the U.S. clinics showed relative intakes of fat and saturated fatty acids to be lower and carbohydrate higher than in the United States. Ischemic heart disease incidence and mortality in Israeli ethnic groups correlated well with group mean total cholesterol values.

The results of the Jerusalem study will be published as a monograph of the Israel Journal of Medical Sciences. Preparation of data analyses for this publication was the major effort during FY 1982. The monograph will describe lipid and lipoprotein profiles by country of origin, dietary



patterns, sociodemographic characteristics in relation to various cardiovascular risk factors, and distribution and characteristics of dyslipoproteinemias in the Jerusalem population.

Collaborative analyses comparing U.S. and Israeli data were begun in September 1982 following the site visit of a U.S. team to Jerusalem. Priority topics include comparisons of food and nutrient consumption, diet and plasma lipid and lipoprotein associations, incidence of coronary heart disease, and resting and exercise ECG studies.

The NHLBI also supports a joint American-Israeli Migrant Study of like-sex siblings, one of whom migrated to Israel while the other remained in the United States. Approximately 2,400 Israelis and 1,525 North Americans were given a complete physical examination to determine whether differences in cardiovascular risk factors are influenced by genetic and/or environmental factors. Data analyses of this completed study are underway.

## Italy

U.S.-Italy cooperation in cardiovascular research was initiated in 1978 upon the signing of the Joint U.S.-Italy Memorandum of Understanding by the Secretary, DHEW, and the Italian Minister of Health in Rome in November 1977. The Fifth U.S.-Italy Joint Symposium, entitled "Methods of Noninvasive Diagnosis in Cardiovascular Disease," was held in November 1981 in Bethesda, Maryland. The purpose of this meeting was to review currently available noninvasive techniques and to assess their role and future potential in the early diagnosis and monitoring of cardiovascular disease. Discussions of imaging techniques included comparisons of the levels of sensitivity, accuracy, speed, and availability of alternative methods as well as the quality of images and data produced by different procedures.

The noninvasive systems reviewed included technologies capable of structural, functional, biochemical, and mechanical assessment of the cardiovascular system in health and disease. These systems draw on images and computerized data generated by X-ray, radioisotope, ultrasound, and nuclear magnetic resonance approaches that provide information about structures and events within the cardiovascular system. For each technique, the theoretical basis underlying the method, the advantages and disadvantages of the procedure, and its current and potential capabilities to assess changes in the arterial walls were considered. Also, the panel reviewed the potential of each technique to assess the clinical significance of atherosclerotic lesions as evidenced by end organ changes in blood flow, metabolism, perfusion, structure, function, and mechanical properties. These new methods are expected to strengthen preventive and research activities in cardiovascular disease and provide

the necessary information to prove conclusively whether a given drug, dietary regimen, surgical procedure, or other therapeutic approach has a positive effect on the control of this disease.

During FY 1982, an Italian exchange fellow worked for 3 months in the laboratory of a U.S. scientist. The joint collaboration supports the theory that the endothelium may contribute to drug- and hormone-induced vasodilation, perhaps through the release of an unidentified endogenous vasodilator. The investigation is aimed at determining the vascular site of action of hydralazine, a widely used vasodilator and anti-hypertensive agent. The results of this collaborative study indicate that the endothelium may play an important role in the vasodilator effect of hydralazine.

The Italian coordinator for the U.S.-Italy exchange program visited the NHLBI in 1982 to discuss plans for the next joint symposium scheduled for the fall of 1983 entitled "Endpoints for Cardiovascular Drug Studies," with presentations addressing chemical, epidemiological, and direct observation endpoints. The proceedings of the U.S.-Italy Joint Symposium on Nutrition and Cardiovascular Disease are being published by S. Karger AG, Basel.

A U.S. exchange fellow will work in Italy from September to November 1982 to continue the joint work on the blood vessel wall in hypertension with his Italian counterpart. The visit represents a unique opportunity to study this problem by means of a bioassay that the Italian scientist has developed and refined, a "superfusion bioassay system" capable of detecting extremely low concentrations of substances with musclop-tropic activity.

## Japan

U.S. and Japanese scientists have enjoyed a long history of successful informal cooperation in the study of cardiovascular diseases. Hypertension is a major problem in both countries, but in Japan the most prevalent sequela is stroke, while in the United States heart attack is the most frequent outcome. Another point of contrast is in the lipid levels of the two populations, which have been increasing steadily in Japan but declining in the United States during the last decade. The study of these differences is the main focus of U.S.-Japanese collaboration.

A U.S.-Japan Umbrella Agreement in Science and Technology in Non-Energy Areas was signed in 1980 and includes cooperation in research on cardiovascular disease. The agreement provides a mechanism for formalizing and expanding the joint research that has been in progress between the two countries for over a decade. In February 1982, in the first official meeting under the 1980 agreement, Japanese and U.S. scientists met to discuss and plan the joint activities. Five topics were agreed upon for joint investigation: further



promotion of information exchanges on epidemiological and experimental studies of hypertension; experimental research on the prevention of hypertensive diseases, especially nutritional prevention and its mechanisms; epidemiological analyses on hypertension and related cardiovascular diseases, including the evolution of hypercholesterolemia and hypertension in the young, and comparison of cerebrovascular and cardiovascular diseases; epidemiological analyses of risk factors, especially dietary risk factors and studies of applicable standardized methodology for assessment of nutritional intake; and further exchange of information on community health control programs and intervention studies, including dietary modification of blood pressure control.

The next U.S.-Japan meeting will be held in December 1982 in Japan, where the focus will be on discussions of problems in standardizing epidemiological and nutritional studies of hypertension, as well as experimental studies on the prevention of hypertension through nutrition control. A joint symposium now planned will give U.S. scientists a broader view of Japanese research in the field.

Japanese scientists have developed several important animal models for studying hypertension, atherosclerosis, and hyperlipidemia. Recent interest has focused on the Watanabe Hereditary Hyperlipidemic rabbit, a particularly good model for studying familial hypercholesterolemia. In 1982, NHLBI scientists initiated contacts with their Japanese counterparts to explore the possibility of further joint study of this model.

NHLBI and Japanese scientists have collaborated since 1966 on studies involving the Stroke-Prone Spontaneously Hypertensive Rat (SHR-SP), a model originally developed in Japan. SHR-SP animals that were fed the standard NIH rat diet had a considerably lower incidence of stroke than rats of the same strain that were fed the standard Japanese diet. The main difference in the diets was in their protein content, and the "stroke protection" may be due to an increased intake of certain sulphur-containing amino acids and aromatic amino acids. Recent human epidemiological studies in Japan have also shown the importance of dietary protein in the development of stroke. Other investigators are studying the role of sodium (Na) and potassium (K), as well as the Na:K ratio, in the development of hypertension. Japanese and American scientists are cooperating on a continuing project entitled "Experimental Studies and Dietary Prevention of Hypertension and Atherosclerosis," funded by the NHLBI and Japanese research institutes. The Japanese coinvestigator visited the NHLBI in 1982 for joint experiments on the preventive effect of methionine feeding on the subsequent development of hypertensive disease. At the Annual Meeting of the Hypertension Specialized

Centers of Research, he presented some new results on the role of sodium and potassium in hypertension. One of his findings is on salt-accelerated platelet aggregation in general as well as in healthy volunteers with a family history of hypertension.

The Honolulu Heart Program, begun in 1970, is a 10-year study of prospective coronary heart disease and stroke in 8,006 men of Japanese ancestry living in Hawaii. On the basis of 10-year heart disease incidence and mortality data, this population was found to be intermediate between the high levels of a similar cohort living on the U.S. mainland and the lower levels of one living in Japan. However, stroke incidence was three times greater in the native Japanese cohort than in the Honolulu sample. The former group also had a strong negative correlation between cancer (particularly colon cancer) and serum cholesterol levels. A 10-year reexamination of 2,000 men from the Honolulu sample was completed in 1982. Data analyses now underway should shed further light on the relative roles of genetics and environment in the development of cardiovascular disease.

#### Kuwait

An agreement for the U.S.-Kuwait Technical Cooperation Program in Health was signed in May 1981. In its preparation of a National Health Plan, Kuwait is seeking consultant help to develop a National High Blood Pressure Education Program and to carry out epidemiological baseline studies and followup monitoring of the population after disease intervention. Kuwait has a relatively high prevalence of hypertension with a low control rate and a rapidly increasing cardiovascular death rate. A U.S. consultant who visited Kuwait in February 1982 made recommendations for an improved hypertension control program. Next, a Kuwaiti delegation visited the NHLBI in March 1982 to discuss the plans for the project. The visit to Kuwait of an NHLBI representative in April 1982 then resulted in a protocol for improved hypertension control. The goals of this effort are to reduce deaths and illness associated with uncontrolled hypertension, to reduce the proportion of persons at risk due to elevated blood pressure, to increase the number of health professionals who are trained in the use of the recommended hypertension management protocol, and to increase the Kuwaiti capability to track and evaluate progress in hypertension control.

#### Nigeria

An Agreement for U.S.-Nigeria Cooperation in Biomedical Research was signed in September 1981. Cooperative activities with the NHLBI have been proposed in hypertension and in sickle cell disease.



## Poland

The NHLBI cooperates with Poland under two separate agreements: the U.S.-Polish Agreement for Health Cooperation, signed in 1973, and the U.S.-Poland Collaborative Research Agreement, signed in 1976 and supported by the Marie Skłodowska-Curie Fund. Activities under the second agreement were temporarily suspended during FY 1982 because of the political situation.

Under the 1973 agreement, activities in three cooperative areas devoted to basic, clinical, and epidemiological research continued in FY 1982.

Area 1. Basic Research in Etiological Mechanisms: The Metabolic Fate and Function of Prostacyclin.--Prostacyclin, a vasodilatory prostaglandin produced in the arteries, is thought to be important in preventing the formation of blood clots. Prostaglandins also seem to affect the circulation as mediators of hormone systems; thus, their role in hypertension is under intense investigation. From November 1981 to January 1982, a Polish scientist continued joint pharmacologic research in the United States on platelet aggregation techniques and prostacyclin metabolites. It had previously been reported that an enzyme present in platelets transforms the labile antiaggregatory compound, prostacyclin (PGI<sub>2</sub>), to a more stable compound, 6-keto-PGE<sub>1</sub>. The present study was directed toward characterizing a previously unrecognized intermediate in this pathway. It is hypothesized that the antiaggregatory activity of PGI<sub>2</sub> may be due to this unknown intermediate substance. This work is important to our understanding of thrombosis and to the development of drugs to prevent it.

Area 2. Clinical Research: The Diagnosis and Treatment of Cardiomyopathy.--Plans were made for the U.S. coordinator to spend 1 month in Poland next year for continued joint investigations.

Area 3. Epidemiological Research: The Cardiovascular and Clinical Correlates of High-Density Lipoproteins.--A cooperative study has been set up to explore the differences in cardiovascular disease and risk factor trends between Poland and the United States. Nearly 5,000 men and women aged 35-64 will be screened in Warsaw and Cracow. The U.S. and Polish coordinators met in October 1981 to discuss the proposed study design and protocol; agreement was reached on all the elements that will be studied. A final study protocol is now being developed. Two Polish scientists will visit the United States in the fall of 1982 to learn laboratory standardization procedures and to study methods of lipoprotein measurement for use in the joint study.

Under the U.S.-Poland Collaborative Research Agreement, the NHLBI has supported two sepa-

rate studies. The first of these is the Polish Trial in Multifactorial Prevention of Coronary Heart Disease, part of a WHO-sponsored European trial. During the U.S. coordinator's visit to Poland in May 1982, the results of the preventive program to reduce coronary heart disease risk factors in selected factory workers were obtained and reviewed. The reduction of coronary heart disease risk factors in high-risk men was greater than in the general factory population. Other data analyses are underway.

The second activity in progress under this agreement is the Followup Study of Chronic Nonspecific Respiratory Disease, to be made in Cracow. This 13-year prospective study is expected to yield important data on this disease.

## Spain

A 5-year Treaty of Friendship and Cooperation between Spain and the United States was signed in January 1976 and renewed in FY 1982. The NHLBI has expressed interest in collaboration in cardiovascular diseases and in blood banking and blood resources.

## Sweden

In FY 1982 exchanges between the United States and Sweden focused on bringing U.S. and Swedish investigators together for discussions of data bases of potential interest to both nations. Data on patients with Pi.ZZ emphysema, a very rare disease, have been collected in both countries. By collecting as much information as possible on this combined group of patients, scientists hope to learn more about the course of this disease and the benefits of treatment.

## United Kingdom

During FY 1982 data collection was completed on the British Norwegian Migrant Study, in which 73,884 men and women in the United States, Britain, and Norway were surveyed by mail to determine the prevalence of angina and other cardiorespiratory symptoms. A publication currently in press reports the analysis of factors associated with angina-related mortality. Other research being prepared for publication concerns mortality differentials due to cigarette smoking and mortality differentials due to cardiorespiratory symptoms. Persons remaining in Britain and Norway reported the symptom of angina more frequently than did the migrants to the United States. During a 5-year period following the survey, angina was found to be a strong predictor of cardiovascular mortality. In the absence of angina, the migrants had a mortality rate similar to nonmigrants, regardless of country of origin. However, the British had higher mortality rates from cardiovascular and non-cardiovascular causes than did the Norwegians.



The primary determinant of angina prevalence was found to be migration status. It is believed that those who migrated constitute a healthier group than those who did not migrate.

#### U.S.S.R.

During FY 1982, U.S.-U.S.S.R. cooperation continued under the bilateral health agreement signed in 1972 and renewed in 1977 and 1982. Cooperation is underway in eight areas of mutual interest and need. During the 10 years of cooperation, 544 specialists were exchanged. More than 100 U.S. and Soviet institutions have participated in the exchange, more than 60 in the United States and 40 in the U.S.S.R. Twenty-two joint symposia have been held, and the proceedings have been published (or are being prepared for publication) in both English and Russian. Nearly 700 scientific reports, abstracts, and related articles have been published under the auspices of the exchange.

#### Area 1. Pathogenesis of Atherosclerosis.--

This is a multidisciplinary, multiclinic research program on the metabolism and epidemiology of plasma lipids and lipoproteins as they relate to atherosclerotic disease. The collaboration is an extension of the NHLBI-sponsored Lipid Research Clinics Program; it involves the participation of nine U.S. lipid research clinics and two clinics in the U.S.S.R. (Moscow and Leningrad). In addition to geographic diversity, the populations selected for joint study in both countries cover broad ethnic, occupational, and age ranges making a variety of cross-cultural comparisons possible. Important differences in cardiovascular risk factors between the Soviet and American study populations have emerged. The possible causes of these differences are being explored to clarify further the relationship between cardiovascular risk factors and deaths in both countries.

Extensive information has been collected and analyzed on the prevalence of hyperlipoproteinemia in men ages 40-59. The results were presented at the First Joint Lipoprotein Symposium in May 1981 and will be published in both countries late in 1982. A 5-year followup to determine the cardiovascular status in a selected subsample of these middle-aged men is now in progress. A second prevalence study on a broader population sample, men and women ages 20-69, was initiated in 1978. Subject screening in this phase was completed in May 1982. All the data have been collected by rigorously trained personnel according to common protocols, using highly standardized laboratory and screening techniques.

In May 1982, the results of the first prevalence study on middle-aged U.S. and U.S.S.R. men were presented at the Sixth International Symposium on Atherosclerosis in Berlin. The

distributions of plasma total cholesterol, triglycerides, and high density lipoprotein (HDL) cholesterol differ significantly between the U.S. and U.S.S.R. sample populations. Both the 40-49 and 50-59 year age groups in the U.S.S.R. had significantly higher mean values for plasma total cholesterol and significantly lower mean plasma triglyceride values. The higher mean levels of plasma total cholesterol in the U.S.S.R. sample may be attributable in part to the higher consumption of dietary cholesterol and saturated fat and to the lower consumption of polyunsaturated fat in that country compared to the United States. This difference in consumption patterns may also account for the higher triglyceride levels found in the U.S. sample. Both U.S.S.R. age groups also had significantly higher HDL cholesterol levels. This form of cholesterol has been associated with a decreased risk of coronary heart disease. The U.S.S.R. 40-49 year age group also had significantly higher mean low density lipoprotein (LDL) cholesterol values. LDL has a strong positive relationship to coronary heart disease. The higher mean HDL cholesterol levels in the U.S.S.R. may reflect an aggregate of environmental factors.

The association of HDL cholesterol with other cardiovascular risk factors was also studied. In both countries, lower HDL cholesterol levels were associated with obesity and carbohydrate consumption, while moderate alcohol consumption was associated with higher levels. Other population studies have demonstrated that HDL cholesterol levels are lower in cigarette smokers than in nonsmokers. The findings here show that the U.S. data support this link, while in the Soviet men the association was either nonsignificant or weak. Further investigation of these differences is planned.

During the visit of a U.S. scientist to the U.S.S.R. in November 1981, drafts of three joint manuscripts were developed from data presented at the First Joint Lipoprotein Symposium. Data analysis is also underway on blood pressure, clinical chemistry tests, smoking, and exercise electrocardiogram findings. A paper entitled "U.S.S.R. and U.S. Nutrient Intake, Plasma Lipids, Lipoproteins, and Nutrients in Men Ages 40-59 Sampled From Lipid Research Clinics (LRC) Populations" will be presented at the American Heart Association meetings in November 1982. The findings show that the Soviet men had higher dietary intake of kilocalories, saturated fats, cholesterol, and carbohydrates, while the American men had greater values for protein, fat, and polyunsaturated fatty acids.

A U.S. working group visited Moscow and Leningrad in December 1981 to review screening procedures in the prevalence study; data collection and mortality classification procedures in the followup study were also discussed. A Soviet biochemist visited the United States for 2 months to work on independent studies of HDL



subfractionation and on the composition and function of HDL apoproteins.

The large investment of resources in this collaborative area is now producing tangible results. Eight years of data collection have culminated this year in the completion of subject screening and observation of important contrasts between the U.S. and U.S.S.R. study populations. Future plans include continued analysis of data from the second prevalence study and continuation of the 5-year followup study. A new emphasis on basic research is planned to investigate questions raised by the epidemiological findings. Directions for this research will be developed at the next Joint Steering Committee meeting.

Area 2. Management of Ischemic Heart Disease.--During FY 1982, cooperation continued on the collection and analysis of data on American and Soviet patients participating in joint studies of different approaches to the management of advanced coronary heart disease. The therapies under investigation include "differential" intensive medical management in the U.S.S.R., "conventional" standardized medical management in both countries, and coronary bypass surgery in the United States. The study includes a total of 1,648 patients carefully selected according to joint criteria. Approximately one-third of the patients are from the Soviet Union, and two-thirds are from the United States.

One group of patients in both the United States and the U.S.S.R. is precisely described by symptoms, coronary angiograms, and a variety of other characteristics. These patients, who constitute the "reference" groups, are being treated by conventional methods. Another group of patients with somewhat different coronary angiographic characteristics is being treated in the United States by coronary artery surgery and in the U.S.S.R. by differential "intensive" medical management. The "reference" group in each country and the two "intensively treated" groups are each composed of men from 30 to 60 years of age. In the United States, the joint study includes analysis of data from patients undergoing surgical treatment who have one or more coronary arteries occluded by lesions causing an obstruction greater than 70 percent. In the Soviet Union, data are analyzed from patients with comparable heart disease who are treated by a specialized pharmacological regimen.

The joint study of these American and Soviet patients will assess whether subjects in the reference group in both countries, who met the same criteria and are treated in a generally similar fashion, have similar characteristics on admission and similar outcome on long-term followup. If this similarity does exist, then there will be a basis for comparing the long-term effects of surgery in the United States with

differential intensive medical care in the U.S.S.R. in the intensively treated patient groups who also share similar initial characteristics.

The data on all patients in both the United States and the U.S.S.R. are stored in the computer facilities at the Data Coordinating Center in Seattle. The study protocol specifies patient followup through June 1983. Followup data on the clinical status of the sample are forwarded to the Coordinating Center twice a year. Completion of initial analyses of the data is anticipated by the fall of 1982 when a joint working meeting will be held in Moscow. Those attending this meeting will review and evaluate the data from the joint study, interpret preliminary results, and discuss opportunities for further cooperation.

Area 3. Myocardial Metabolism.--Basic research to develop information that may lead to improved methods for prevention and treatment of cardiac diseases is the objective of Area 3. Joint studies are underway on the mechanisms of energy transfer within cardiac cells and on the ways that these cells respond to oxygen deficiency. Other studies concern the factors that regulate cardiac growth, the coordination of contraction within cardiac cells, the response of cardiac cells to changes in their microenvironment, the visualization of cardiac muscle damage due to oxygen deficiency, and the effective rapid transport of drugs to damaged heart muscle.

Teams of American and Soviet collaborators have carried out joint research projects spanning a number of years. The research is carried out jointly in U.S. and U.S.S.R. laboratories, enabling both sides to contribute techniques unique to their respective countries. As a result, new information has become available more rapidly than would have been possible without such cooperation. The English language proceedings of the Fifth U.S.-U.S.S.R. Symposium, which were published in FY 1982, contain reports on the cooperative projects. Also during this year, several joint articles have appeared in major U.S. and Soviet journals. Titles include "Ca<sup>2+</sup>-Dependent Interaction of 5-Dimethylaminonaphthalene-1-Sulfonyl Calmodulin with Cyclic Nucleotide Phosphodiesterase Calcineurin and Troponin I," "A Study of Actin Fibronectin Interaction," "Chromatographic Studies on Interconversions of 'Non-Activated' and 'Activated' Forms of Glucocorticoid Receptor Complexes from Rat Heart Cytosol," and "A Structural Study of Filamin, a High-Molecular-Weight Actin-Binding Protein From Chicken Gizzard."

Three U.S. scientists conducted joint research in the U.S.S.R. in FY 1982. One worked on lipoprotein genes and on the effect of glucocorticoids on myocardial calcium metabolism. Joint research protocols were drafted, and a



jointly authored article was prepared. The second U.S. scientist continued joint research and completed a joint publication, entitled "Creatine Kinase of Heart Mitochondria: Changes in Its Kinetic Properties Induced by Coupling to Oxidative Phosphorylation." Both scientists made presentations at the Ninth World Congress of Cardiology in Moscow. A third U.S. scientist continued joint work on structural proteins of cells, including studies on spectrin. He prepared and took to the Soviet Union a large quantity of pure spectrin, a cytoskeletal protein of red blood cells. The collaborating Soviet scientist conducted physical chemistry studies on this protein.

Two Soviet scientists visited the United States during FY 1982. One continued joint studies on targeted drug transport to damaged cardiac cells employing drug-loaded liposomes. In 1978, the Soviet investigator together with a U.S. colleague succeeded in linking antibodies specific for cardiac myosin to liposomes. When cardiac muscle is damaged by lack of oxygen, intracellular antigens are uncovered that are recognized by this liposome-antibody complex. By adding an isotopic marker to the drug liposome complex, scientists can visualize the damaged muscle at the same time as the therapeutic agent is rapidly and preferentially applied to it. Results of these joint studies have been published in major U.S. and Soviet journals. A second application of the Soviet-developed liposomes is being studied both in the United States and the U.S.S.R. A U.S. biochemist has synthesized a potent renin inhibitor to be used as a potential antihypertensive agent. However, this peptide is metabolized within minutes after injection into laboratory animals. It is hoped that this breakdown of the active compound can be delayed by encapsulating it into liposomes. The U.S.-developed peptide has been sent to the U.S.S.R., where it will be linked to liposomes. These collaborative studies are aimed at the development of a long-acting injectable renin inhibitor suitable for use in the treatment of hypertension. The other Soviet scientist studied advanced nuclear magnetic resonance techniques to measure metabolism in the intact heart and to begin a joint research project in this area.

Three senior U.S. investigators visited the U.S.S.R. in 1982 to present papers and exchange research findings in areas of mutual interest. The topics included regulation of protein turnover in skeletal and heart muscle, regulation of amino-acid catabolism, regulation of microtubule assembly and distribution in eukaryotic cells, calcium regulation of cytoskeletal functions, mechanisms of mitosis and chromosome movement in eukaryotic cells, molecular differentiation of the myocardium, and the mechanism of heart morphogenesis. Also, the U.S. coordinator for Area 3 visited the U.S.S.R. to plan the next joint symposium to be held there in 1983.

Area 4. Congenital Heart Disease.-- Cooperative activities in this area center on the surgical treatment of complex heart defects as well as on methods of diagnosis and postoperative care to reduce mortality from congenital heart disease.

A three-member Soviet delegation including the U.S.S.R. Coordinator for Area 4 visited the United States and met with U.S. counterparts to discuss plans for further cooperation and to review the results of the latest research on this cardiovascular disease problem. Plans were made for the Fifth Joint U.S.-U.S.S.R. Symposium on Congenital Heart Disease to be held in May 1983 in the United States.

Surgical techniques were discussed during the delegation's visit to U.S. clinics and cardiovascular centers. Both sides reviewed their experiences with heart transplants and surgical procedures to control arrhythmia. The Soviets have an active surgical program for arrhythmia, and interest was expressed in joint discussions of indications for surgery and also of valve replacement as possible topics for future joint collaborative activities.

In July 1982, a U.S. scientist visited the U.S.S.R. to meet with the U.S.S.R. Coordinator for joint discussions on cardiorespiratory physiology and postoperative care. He lectured at Soviet medical institutions on the topics of acute respiratory failure, postoperative respiratory failure, and general principles of intensive care of the critically ill patient.

Area 5. Sudden Death.--A disturbance in heart rhythm is believed to be the immediate mechanism of sudden death, which constitutes a leading cause of mortality in the United States as well as in the U.S.S.R. U.S.-U.S.S.R. collaboration is designed to learn more about the mechanisms of arrhythmias and about the intervention of antiarrhythmic agents to regulate the heart's electrophysiologic functions.

During FY 1982, joint activities included the Third Joint U.S.-U.S.S.R. Symposium on Sudden Death held in Kaunas, Lithuania, June 1982. In December 1981, the U.S.S.R. coordinator and his colleague from Kaunas visited the United States to complete plans for the symposium. An eight-member U.S. delegation participated in the symposium and also attended the Ninth World Congress of Cardiology in Moscow. Symposium topics included recognition of risk associated with arrhythmias, reversible coronary artery obstruction, pathobiology of acute myocardial ischemia, sensory functions of the heart, modulation of adrenergic activity of the heart, variations in morphology of the atrioventricular node and His bundle of the human heart, neurological and humoral aspects of sudden death, and the possible protective effect of neuropeptides in animals susceptible to sudden death when placed in conflict situations. A joint paper was pre-



sented on an ongoing exchange of epidemiological data to determine if certain populations in each country may provide a "laboratory" for investigating national mortality trends in each country. The U.S. investigators had learned that in local areas time trends of the incidence of acute myocardial infarction, one of the most important clinical components of ischemic heart disease (IHD), parallel national mortality trends. The joint presentation reported the results of investigations of data from medical histories and from clinical, electrocardiogram, and laboratory studies of patients with acute myocardial infarction in Oakland, California, and compared these data with those of patients included in the registry of acute myocardial infarction in Kaunas, Lithuania. A number of differences were noted in electrocardiographic and serum enzyme studies. Nevertheless, percentages of cases classified as definite and possible acute myocardial infarction among the U.S. and Kaunas patients were similar. Through the study and comparison of long-term trends in the two nations, we expect a better understanding of the factors affecting development of ischemic heart disease and sudden death.

Further exchanges of scientists are planned in six areas: pathological anatomy, electrophysiology of sudden death, study of the effects of antiarrhythmic drugs, clinical aspects of sudden death, epidemiology of sudden death, and higher nervous and peripheral nervous activity in ventricular arrhythmias and sudden death.

Area 6. Blood Transfusion.--The exchange in Area 6 focuses on research on blood and blood products for transfusion and treatment of disease. In the past, the emphasis in Area 6 has been on hepatitis, posttransfusion hematological complications, and blood substitutes. However, in recent years the range of collaboration has broadened, encompassing thrombosis and hemostasis in general, with particular emphasis on platelet abnormalities as well as on hemophilia and other genetic bleeding disorders.

In December 1981, a three-member Soviet delegation visited the United States to exchange information and data on procedures for blood donor processing, blood components, and preparation of platelet concentrations. U.S. and Soviet scientists discussed a possible joint project for isolating and studying vesicles shed by red cells during storage and for quantitative analysis of their membrane proteins. It was agreed that prior to shipping specimens from the U.S.S.R. to the United States, preliminary studies on the stability of vesicle preparations would be completed in Moscow. In the area of hepatitis, the Soviets are studying the specific immunology of anti-A as well as anti-B hepatitis. The visit of the Soviet delegation provided opportunities to discuss future collaboration on the use of Factor VIII in the treat-

ment of hemophilia, red blood cell preservation, and long-term preservation of platelets.

A U.S. scientist visited the Soviet Union in April 1982 to lecture on genetics and hemoglobinopathies and to discuss modern laboratory techniques of gene manipulation. The visit provided an opportunity for the Soviet Central Institute of Hematology and Blood Transfusion and the NHLBI to exchange information on current developments in molecular biology research on thalassemia and to plan future collaborative activities.

During the fall of 1982, a U.S. scientist visited the U.S.S.R. to continue joint studies in the area of hematapheresis. This collaboration compared platelet collection procedures and patient transfusion response to platelets collected by continuous flow cell separation techniques; compared recipient response to leukocyte-rich single donor platelets ("Aminco") and leukocyte-depleted platelet ("IBM-2997") concentrates and patient response; measured efficiency of cyto-reduction procedures using "Aminco" and "IBM-2997" blood cell separators in patients with blood diseases (thrombocytosis and leukocytosis); and determined the frequency of leukapheresis and platelet pheresis to reduce risks of cerebrovascular accidents.

The new U.S.S.R. chairman for Area 6 and his U.S. counterpart met in August 1982 during meetings of the International Hematology and Blood Transfusion Societies to discuss plans for exchanges and studies. These plans will be developed further during the Ninth Working Meeting in Area 6 scheduled for December 1982 in the United States. At that time, the U.S. and U.S.S.R. representatives will also plan the proposed program of the Third Joint Symposium on Blood Transfusion to be held in the U.S.S.R. in 1983.

Area 7. Hypertension.--Begun in 1977, joint activities in this area have focused on the exchange of information, exchanges of scientists, joint working meetings, and joint symposia on the clinical, psychophysiological, behavioral, epidemiological, and preventive aspects of hypertension.

The Proceedings of the 1981 Joint U.S.-U.S.S.R. Symposium on Hypertension: Biobehavioral and Epidemiological Aspects are currently being prepared by the U.S. side for publication in English and by the Soviet side for publication in Russian. They will include 10 Soviet papers and 7 U.S. papers.

In July 1982, two U.S. scientists visited the U.S.S.R. to develop plans for a joint study on psychological interventions and the role of the sympathetic nervous system in primary hypertension. This collaborative study assesses neuroendocrine and blood pressure changes resulting from biobehavioral treatment strategies. Specifically, the study will determine if nonpharm-



acological interventions (hypnosis, biofeedback, transcendental meditation, and relaxation techniques developed by the Soviet side) can reduce blood pressure in patients with primary hypertension classified according to psychological profiles developed in the United States.

In accordance with the Summary of Discussions signed at the 1981 symposium, a joint working meeting on biobehavioral treatment of hypertension is scheduled for the fall of 1982 in the U.S.S.R. Three topics of collaboration are being developed in this area--basic, clinical, and community intervention studies. In each of these areas, resource groups of experts have been identified to facilitate future scientific exchanges and to develop a productive exchange program between U.S. and Soviet laboratories.

**Area 8. Artificial Heart Research and Development.**--U.S.-U.S.S.R. collaboration in the development of artificial heart and circulatory assist systems recognizes that present and foreseeable treatments still leave a substantial number of patients with compromised or fatally impaired heart function. The development of supportive mechanical devices to assume some and eventually all of the pumping function of the failing heart is the long-term goal of this cooperation.

During April 1982, the U.S.S.R. Chairman for Artificial Heart Research and Development visited the United States to discuss mechanically assisted circulation. Six areas of proposed cooperation were identified: the study of the mechanisms of interaction of biomaterials with blood and its components and the development of comparability criteria for evaluating biomaterials' hemocompatibility; comparative evaluation of the condition of the myocardium by means of biochemical and morphological tests during one- or two-sided bypass; comparative evaluation and development of new methods of connecting various pump devices for two-sided bypass; exchanges of specialists and delegations in order to continue further joint activities in assisted circulation, artificial heart control systems, and biomaterials; publication of joint articles on U.S.-U.S.S.R. activities and scientific data exchanges; and plans for the Third and Fourth U.S.-U.S.S.R. Symposia on Artificial Heart and Assisted Circulation in the U.S.S.R. in 1983 and in the United States in 1985.

Two publications were generated from U.S.-U.S.S.R. cooperation in this area during FY 1982. A joint paper entitled "In Vitro Evaluation of U.S. and U.S.S.R. Artificial Hearts" was published in Artificial Organs, the journal of the International Society of Artificial Organs, in May 1982. A Soviet article describing an implantable artificial heart driven by a compact motor was received by the U.S. side and translated for review by U.S. investigators.

In accordance with a previous agreement, the

U.S. side provided the U.S.S.R. counterparts with biomaterials in exchange for the control system received from the U.S.S.R. in 1981. Plans for the future call for continued exchanges of scientists from each side to conduct joint in-depth evaluation of the blood compatibility of several frequently used biomedical polymers by means of in vitro techniques.

One of the outcomes of U.S.-U.S.S.R. cooperation in the cardiovascular area is the publication of the Journal of Soviet Cardiovascular Research, published by Plenum Press. This English language journal, now in its third year of publication, contains articles translated from Kardiologia and other Soviet journals on the best Soviet research in the cardiovascular area. Articles are selected by an editorial board composed of U.S. and Soviet scientists, including several of the coordinators for the eight areas of U.S.-U.S.S.R. cooperation in the cardiovascular field.

### Venezuela

A Joint U.S.-Venezuela Science and Technology Agreement was signed in October 1979. Venezuelan scientists have a strong interest in cooperation in the cardiovascular area, particularly in clinical research. Possible collaborative efforts are being considered in Chagas' disease, which is endemic in rural areas of Venezuela and in other South American countries. Chagas' disease infects children at an early age, and a large proportion of these patients develop cardiomyopathy several years later.

Venezuelan and NHLBI investigators are developing a protocol to study Chagas' disease. During FY 1982, the director of the Venezuelan institute established to prevent, detect, and treat this disease worked with NHLBI epidemiologists on protocol development, data handling methodology, and the design of instruments to be used in this study. Later in FY 1982, the Director, Centro Pan Americano de la Investigacion y Adiestramiento de Enfermedades Tropicales (CEPIALET), who is also the Venezuelan coordinator for the U.S.A.-Venezuela Cooperative Agreement, visited the NHLBI to discuss the Chagas' project with Institute staff.

Venezuela is one of the countries interested in developing uniform international standards for the biomaterials used for human prostheses. To facilitate both national and international standardization, the NHLBI has produced biomaterial standards for distribution to interested investigators. Samples of these U.S. biomaterial standards have been requested by Venezuelan investigators.

### Yugoslavia

Coronary heart disease (CHD) can result from the interaction of a number of environmental,



behavioral, genetic, and physiological factors. Because Yugoslavia is undergoing rapid industrialization, scientists are concerned about increased coronary heart disease.

Several studies on this problem have begun as a result of the agreement signed between the United States and Yugoslavia in 1973. During FY 1982, plans were completed for a study entitled "An Epidemiological Study of Secular Trends in CHD Risk Factors." This study uses data from a population in Tuzla, a suburb of Zagreb, previously studied for many years under the project "Incidence of Hypertension and Coronary Heart Disease." The objectives of the new study are to determine whether cigarette smoking, hypertension, and electrocardiographic abnormalities are increasing in Yugoslavia. The study will include a repeat examination of part of the original cohort in Tuzla, as well as an examination of two younger cohorts (aged 35-44), one in Tuzla and one in Belgrade. Two U.S. scientists visited Yugoslavia in April and May 1982 to discuss technical aspects of the study to ensure comparability of the Yugoslav data with U.S. data. The computer capabilities of the Institute of Chronic Diseases and Gerontology in Belgrade were reviewed as well as procedures for data analysis.

By measuring risk factors over an extended period of time in cohorts of similar age, this study will examine whether the industrialization and urbanization process is accompanied by changes in physiological characteristics. It will also provide information on changes in the prevalence of CHD. If an increase in CHD is observed, the study will ascertain how much might be due to changes in the known risk factors. The study will also seek to determine which changes in the study population's environment are the most important for developing CHD.

### **Cooperation With International Agencies**

During FY 1982, the NHLBI continued its active cooperation with international agencies. Since 1980, the Institute has been a WHO Regional Collaborative Center for Research and Training in Cardiovascular Diseases for the Americas. In this capacity, the NHLBI provides advisory services for WHO, and collects and exchanges information on cardiovascular diseases. The Institute also assists in the placement of WHO-sponsored fellows from different countries.

The NHLBI is collaborating with WHO on the Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA), a new health information system to measure heart disease incidence by collecting longitudinal, cross-cultural data on cardiovascular disease risk factors. NHLBI epidemiologists assisted in designing the study protocol. Pilot studies were completed in 1981 in four communities where

the formal study is now underway. Other MONICA's will be launched in 1983 in eight additional countries.

Plans for other cooperative activities between the NHLBI and WHO were considered. In July 1982, the WHO representative for genetic diseases met with NHLBI staff to discuss possible future collaboration on sickle cell disease. WHO is interested in implementing programs in Africa to address this problem. The Chief of Cardiovascular Diseases at WHO visited the NHLBI in April 1982 to discuss areas of continuing cooperation. The Assistant Director for International Programs, NHLBI, met with WHO officials in Geneva to discuss its programs on cardiovascular disease prevention and control.

The NHLBI and WHO have also exchanged information concerning WHO's Integrated Program for the Prevention and Control of Noncommunicable Diseases. The objective of this program is to improve the health of total communities with respect to noncommunicable diseases through an integrated approach to health promotion. The NHLBI has provided WHO with information on its intervention and health education programs relevant to the WHO effort.

At the request of PAHO, Institute staff participated in a workshop entitled "Contribution of Dietary and Pharmacological Interventions in the Prevention and Control of Cardiovascular Diseases" in March 1982. This workshop brought together investigators from Brazil, Chile, Ecuador, Jamaica, Mexico, and Trinidad to plan the project. Responding to a number of questions regarding the proposed design of the study, Institute staff gave advice based on Institute experience with similar projects. Among the questions discussed was the strength of the evidence that an increased intake of polyunsaturated fatty acids coupled with a decreased intake of saturated fatty acids to bring the dietary ratio close to 1 (P/S ratio = 1) results in both lowering blood pressure (systolic and diastolic) in normal as well as in mildly hypertensive populations and reducing the tendency to thrombosis.

Two PAHO fellows from Thailand visited the NHLBI in May 1982, one of whom is the Chairman for Planning and Organization for Prevention and Control of Cardiovascular Disease in Thailand. They toured U.S. medical and research facilities to study the planning, organization, and research aspects of the prevention and control of cardiovascular disease. Also, in FY 1982 two U.S. scientists--one individually and the other as part of a WHO team--visited Thailand to continue joint scientific discussions.

### **Extramural Programs**

During FY 1982, the NHLBI awarded 6 contracts and 17 grants to the following countries: Argentina, Australia, Canada, Denmark, Israel,



Romania, and Sweden. These awards supported mainly cooperative epidemiological studies on foreign components of national clinical trials. Ten fellowships were awarded to U.S. scientists for training in the following countries: Belgium, Canada, Israel, Sweden, Switzerland, and the United Kingdom. These young American researchers took their training outside the United States to capitalize on unique research opportunities available in chosen foreign institutions.

Human red blood cell production is basically under the control of the erythropoietin hormone. Extensive studies of this hormone are underway in the United States. These studies require human erythropoietin, which is best obtained from the urine of anemic patients. In certain areas of Argentina, iron-deficient anemia due to hookworm is endemic. The NHLBI is supporting the collection, purification, and study of this hormone from these patients. The Institute also makes available erythropoietin for study by U.S. researchers.

The Institute is supporting research on the genetic epidemiology of precursors of human hypertension in a migrant Polynesian population. This longitudinal study is designed to identify factors that cause an increase in blood pressure, lipid levels, obesity, and other risk factors of cardiovascular disease. The Tokelu Island Migrant Study is an epidemiologically based investigation of the changes in physical and socio-cultural environment that are associated with increased risk of cardiovascular disease, as Tokelauans migrate from their traditional atolls to New Zealand. The study is unique in that the population was surveyed before migration was completed in 1968 and both the nonmigrant population (in Tokelu) and the migrant population (in New Zealand) are subject to longitudinal followup. Migrants showed a considerable increase in the prevalence of hypertension and a less marked increase in mean blood pressure. Obesity, which is increased in the migrants, is clearly a factor in their elevated blood pressure.

### **International Conferences, Seminars, and Meetings**

A conference titled "Nutrition and Blood Pressure Control: Current Status of Dietary Factors and Hypertension" was held in September 1982. NHLBI staff chaired several sessions, and NHLBI grants and contracts supported the research of many of the speakers. The symposium provided a forum for communication among health professionals, biomedical investigators, and representatives of government and industry. Scientists from Canada, the Federal Republic of Germany, Japan, the Netherlands, and the United Kingdom took part in the discussions. The role of sodium, potassium, divalent ions (calcium,

magnesium, selenium, and other trace elements) on blood pressure was discussed. Other topics covered were the effects of macronutrients, alcohol, lipids, and carbohydrates on blood pressure and diet as opposed to drug therapy for hypertension.

An international workshop, "Changing Patterns in Cardiovascular Disease in the Pacific Basin," was sponsored in January 1982 by the NHLBI in Kona, Hawaii. Areas represented were Australia, China, Fiji, Hawaii, Japan, Micronesia, Nauru, Niue, New Zealand, the Philippines, Rarotonga, Western Samoa, the United Kingdom, the United States, and Taiwan. Approximately 35 scientists and observers attended this workshop. Topics included stroke risk factors such as salt, blood pressure, and smoking; and demographic and socioeconomic factors of CHD, rheumatic fever and rheumatic heart disease, sudden death, and diabetes. The Pacific Basin region offers a unique opportunity to study how environmental and genetic factors interact to influence the risk of coronary heart disease, stroke, and hypertension. Of particular interest is the comparison of cardiovascular risk due to patterns of migration.

"Implications of Recent Beta-Blocker Trials for Post Myocardial Infarction (MI) Patients," a workshop held at the NHLBI in May 1982, reviewed and documented the state of knowledge regarding the effects of beta-blocking agents in post-MI patients to generate recommendations for future research on beta-blocking agents and to address questions regarding the implications of recent beta-blocker trials. Results from ongoing long-term beta-blocker trials in Australia, the Federal Republic of Germany, the Netherlands, Sweden, the United Kingdom, and the United States were compared. Experts from Ireland, Norway, Sweden, the United Kingdom, and the United States presented findings on the beneficial effects of administering these drugs following an acute heart attack. The U.S. participants presented the results of a randomized trial of propranolol in patients with acute MI. Thirty-six months following their acute MI, patients receiving propranolol had a survival rate significantly greater than that of a matched group of patients receiving a placebo. The Swedish workers reported similar favorable results with metoprolol, another beta-blocker.

### **Intramural Programs and Activities**

Joint research was carried out in laboratories of the Division of Intramural Research, NHLBI, by 63 foreign investigators who came from Australia, Canada, China, the Federal Republic of Germany, France, Greece, Hong Kong, India, Ireland, Italy, Jamaica, Japan, Korea, Poland, Sweden, Turkey, the United Kingdom, and Taiwan.

The NHLBI intramural scientists and their French counterparts have been undertaking joint studies on the pathology of interstitial lung diseases (see France). These studies have proven valuable to both sides because they allowed pooling of scarce lung biopsy material from patients in both countries.

Active research cooperation of NHLBI intramural scientists with their Japanese colleagues has taken place since 1966 (see Japan). This cooperative research is investigating the interrelationship of nutrition, hypertension, and

stroke; the researchers are using animal models of hypertension, stroke, and hyperlipidemia developed in Japan. These rat models of human disease have provided much new information on the basic etiology of these important diseases.

A scientist from the Biochemical Pharmacology Section, NHLBI, conducted joint work in Australia to determine the role of the brain serotonergic system in the regulation of arterial blood pressure, and on techniques, including immunohistochemistry, applicable to the study of blood pressure.



# Chapter VI

## National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

### Introduction

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) conducts and supports biomedical research in a wide range of mostly chronic, often disabling, disorders. In many instances, these activities benefit from the contributions of members of the international scientific community. Continued collaboration with international scientists, in addition to funding of research with the potential for worldwide impact, remains an established priority for the Institute.

Ongoing international programs of the Institute are targeted at such areas as nutrition, arthritis, and thyroid hormone synthesis. Regarding international cooperation on nutrition, the Institute expects to increase an understanding of the influence of the environment on nutritional requirements; on the interaction of nutrition, immune competence, and infection; and on the health consequences of dietary patterns. In the area of arthritis collaboration, one goal is to ascertain the best drugs to treat juvenile rheumatoid arthritis. Cooperation in research into thyroid hormone synthesis might result in an improved treatment of hypothyroidism.

Through international cooperation and collaboration in areas such as these, scientists may perhaps control, prevent, and ultimately eliminate the many chronic and disabling disorders falling within the purview of the Institute.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

Through the Bilateral Cooperative Agreements Program, the NIADDK has developed collaborative and cooperative activities with France, Japan, and the U.S.S.R. These activities consist of the U.S.-Japan Malnutrition Panel Research Support Program, the U.S.-U.S.S.R. Cooperative Program in Arthritis, and the NIH-INSERM Agreement.

The following discussion outlines the status, current activities, and accomplishments of the collaborative programs with the three nations.

#### Japan

The Malnutrition Panel, a binational steering committee of experts, was established in 1966 as part of the U.S.-Japan Cooperative Medical Sciences Program. The entire cooperative program, which covers a number of different disease areas, is administered by the NIAID, but the malnutrition portion is the responsibility of the NIADDK Division of Digestive Diseases and Nutrition, with significant support from the NICHD.

Malnutrition continues to be a serious problem in most Asian countries, the most common forms of which are protein-calorie malnutrition and deficiencies of iron and vitamin A. Also of concern are various disease states, particularly diarrheal infections, that impair the body's utilization of some nutrients or lead to the excessive loss of others. These infections are the major cause of death in children under 5 years of age. Undernutrition also has a severely adverse effect on the outcome of pregnancy, increasing the number of infants born prematurely or with low birth weight and with more disabilities and inadequate nutritional reserves. Iron deficiency, a widespread disorder in Asia, causes anemia and all its attendant symptoms. It may also interfere with normal immune responses and may lower resistance to infection. Vitamin A deficiency is responsible each year for many thousands of cases of impaired vision and total blindness in children.

The five priority areas of focus of the Malnutrition Panel are:

- Influence of environmental and host factors on nutritional requirements;
- Health significance and methods of preventing iron deficiency;
- Interaction of nutrition, immune competence, and infection;

- Effects of nutrition on physical and mental development, behavior, physical capability, and work performance; and
- Health consequences of different (and changing) dietary patterns and food habits.

An announcement was made in FY 1982 regarding the availability of grant support for studies on "Environmental and Host Factors Affecting Nutritional Requirements." In August 1981, a workshop was held in San Diego, California, entitled "Opportunities for Collaborative Research Relating to Nutritional Requirements in Asian Countries." In attendance were nutrition scientists from Bangladesh, Burma, China, India, Japan, Malaysia, New Guinea, Thailand, the United Kingdom, and the United States. The U.S. Malnutrition Panel has also collaborated with the Japanese Malnutrition Panel to organize a workshop, "Practical Approaches to Eradication of Subclinical Iron Deficiencies," which was held in Tokyo on December 7 and 8, 1982.

Recent findings from a number of nutrition research grants supported by the NIADDK and other NIH Institutes and identified as relevant to the U.S.-Japan program are listed below:

Zinc.--An important ongoing study at the University of Colorado has shown that low dietary zinc intake is a specific environmental factor that may contribute to poor linear growth velocity in children. This effect was observed in a double-blind controlled study of 40 preschool children. Dietary zinc supplementation significantly increased linear growth velocity in the boys, but not in the girls.

Another study, at the University of Texas, suggests that a zinc-dependent enzyme, RNase, may be an appropriate means of monitoring zinc status in man. A group of young adult men were fed a zinc-deficient diet for 8 weeks, during which the activity of RNase was found to increase significantly in the parotid saliva and blood plasma during zinc depletion and return toward normal with zinc repletion.

Iron.--In a study funded at the University of California at San Francisco, decreased red blood cell (RBC) survival in iron deficiency has been observed in association with increased RBC membrane stiffness. Decreased RBC deformability in iron deficiency was shown to be due primarily to decreased membrane viscoelasticity. Iron-deficient RBC's showed increased susceptibility to peroxidation and showed evidence of spontaneous membrane lipid and protein cross-linking. These conditions suggest that increased RBC membrane stiffness in iron deficiency may be related to peroxide damage and is responsible for the observed decrease in RBC survival.

In other studies on the effect of iron status on immunity in neonatal and maternal rats, results reveal that individual components of the immune response are affected differently by iron deficiency. While circulating immunoglobins (IgG or IgM) are resistant to change, the development of lymphoid organs such as the thymus and spleen is profoundly affected by iron deficiency, which may alter permanently the immunocompetence of the organism.

Vitamin A.--At Tufts University, a rapid dark adaptation test has been developed that can be used under field conditions on children as young as age four. This method, which is very sensitive to vitamin A deficiency, involves matching the intensities of colored discs to the function of the cones in the eye (not rod function), so that under dim lighting conditions the ability to separate the different colored discs is dependent on rod function alone. This rapid dark adaptation test is expected to become widely used in surveys to identify subclinical vitamin A deficiencies.

In other studies relating to vitamin A, two patients with markedly abnormal dark adaptation, despite normal serum vitamin A and zinc levels, experienced restoration of dark adaptation to normal through protein repletion alone (without supplemental vitamin A or zinc). These results argue that protein status does affect the ability of the retina to use vitamin A.

Protein-Energy Requirements.--Studies are underway at Johns Hopkins University to assess the growth, body composition, and protein status of 6- to 36-month old infants on low, medium, or high levels of protein intake in relation to dietary calories (from 4.7 to 8 percent calories from protein). So far, results have not identified significant differences in growth or body composition because the numbers are too small for conclusive analysis. However, overall caloric intake appears to rise progressively as the percent of protein calories decreases. Also, changes in proportion between calculated arm muscle and fat cross-sectional areas favor the highest protein intake group.

At the Massachusetts Institute of Technology, noninvasive stable isotopes ( $^{13}\text{C}$ ,  $^2\text{H}$ ,  $^{15}\text{N}$ ) have been used to investigate the dynamic aspects of whole body amino acid metabolism in adult humans brought about by changes in intake of dietary protein and energy. Results, indicating that the synthesis of alanine is extensive and increases under conditions of low protein and high energy intake, suggest that alanine plays an important role in the retention and recycling of body nitrogen when there is a need to conserve nitrogen. In contrast, changes in glycine metabolism do not appear to affect significantly the maintenance of the whole body nitrogen economy. In addition, this new technique is expected to be of value in determining the requirements



for essential dietary amino acids in human subjects.

#### U.S.S.R.

The U.S.-U.S.S.R. program of cooperation in arthritis originated with the Health Exchange Program of 1972, an agreement to improve collaboration between the two countries in public health and medical service. In September 1973, arthritis became a subject of cooperation under this program. The program has three major divisions: clinical studies in rheumatic disease; studies in the basic science of rheumatic disease; and orthopedic surgery for arthritis, with emphasis on clinical studies, using common, agreed-upon protocols for the treatment of rheumatoid arthritis and systemic lupus erythematosus.

Over 100 subjects in both the United States and the U.S.S.R. are participating in an ongoing trial, begun in August 1981, of the comparative benefits of hydroxychloroquine and D-penicillamine in treating juvenile rheumatoid arthritis.

Another study, at the University of California at Los Angeles, addresses the "Assessment of Methods for Measuring Hand Function in Rheumatoid Arthritis."

#### NIH-INSERM Agreement

Under an agreement between the NIH and INSERM, substantial scientific collaboration has occurred between the Clinical Endocrinology Branch of NIADDK and the Unité de Recherche sur la Glande Thyroïde et la Régulation Hormonale of INSERM. The exchange of scientists between the two centers has provided excellent opportunities for collaborative research and the effective use of trained personnel in the study of thyroid hormone synthesis and metabolism. Investigators from both the United States and France have been working on separate but related aspects of thyroid physiology and biochemistry. Combining some of the resources available to each group has greatly enhanced the progress of research in these areas, and has led to the evolution of new procedures for solving problems of thyroid functions.

In FY 1982, two French scientists engaged in collaborative research in a Clinical Endocrinology Branch laboratory.

#### Extramural Programs

To use the expertise available through biomedical researchers in other countries and to further the progress of knowledge in high-priority health problems of international scope, the NIADDK continues to support projects initiated by scientists located outside the United States who apply directly to the Institute's extramural research programs. In FY 1982, more

than 30 such projects in the form of research grants, postdoctoral training grants, and cooperative agreements were active at the NIADDK.

International research funded by the NIADDK has made many contributions to knowledge, in both the clinical and basic science areas. For example, in the area of end-stage renal disease, work carried on at the University of Helsinki in Finland is attempting to describe the structure of inflammation in experimental and human kidney allograft rejection and to use these findings to develop new diagnostic methods for monitoring and counteracting rejection episodes in clinical transplantation. At the Karolinska Institutet in Sweden, the NIADDK is supporting prospective investigations into the metabolic effects of continuous ambulatory peritoneal dialysis.

Some other current projects abroad relate to diabetes research. Research at Royal Southern Memorial Hospital in Australia is attempting to elucidate the genetic and environmental interactions that make for susceptibility to non-insulin-dependent diabetes mellitus (NIDDM). The objectives of the project are: (1) to determine whether specific genetic markers exist in the NIDDM diabetic or in individuals with predisposing genes for diabetes; (2) to determine whether the differing susceptibility of various ethnic groups to NIDDM is related to the presence or absence of these genetic markers; (3) to establish the relative roles of other factors such as age, nutrient intake, physical activity, obesity, and stress in the causation of NIDDM in genetically susceptible individuals; and (4) to identify possible preventive factors relating to NIDDM in high prevalence populations. The studies will be carried out in Caucasian, Melanesian, Polynesian, Micronesian, and American Indian populations. It is hoped that feasible intervention programs might be defined on the basis of future findings.

A project at the Chaim Sheba Medical School in Tel Hashomer, Israel, is aimed at clarifying the risk factors for human glucose intolerance. The overall objectives are to quantify interrelationships, distinguish between causes and effects, evaluate the relative role of environmental and genetic factors, and understand the temporal sequence of events among glucose intolerance, obesity, and macro- and microvascular complications of diabetes.

#### International Conferences, Seminars, and Meetings

Scientific meetings with an international audience play a major role in the interchange of biomedical information. They provide a forum for the exchange of research findings and information among investigators from different countries, and they often stimulate further sci-



entific collaboration. The NIADDK continues to contribute toward the support of selected conferences within the United States and abroad, providing a setting for scientific cross-fertilization among international investigators.

The International Society for Experimental Hematology (ISEH) held its eleventh annual meeting in Baltimore, Maryland, during August 1982. The ISEH is a relatively young organization, which has grown to more than 500 members in the past 10 years. Meetings are held each year, alternating between the United States and foreign countries, usually in Europe. Topics presented at the Baltimore meeting included bone marrow transplantation, hematopoietic stem cell regulation, erythropoiesis, granulopoiesis, lymphopoiesis, effect of radiation on stem cells, animal models for human hematopoietic disorders, and effects of aging on the hematopoietic system. At past meetings of the ISEH, presentations have been made by scientists from such countries as Australia, Finland, the Federal Republic of Germany, Israel, the Netherlands, the United Kingdom, and Yugoslavia. As a focus for the initial presentation of work from laboratories around the world, the annual meetings of the ISEH are an important mechanism of international scientific exchange.

The NIADDK provided major support for the Third International Congress on Nutrition and Metabolism in Renal Diseases, which was held in Marseilles, France, in September 1982. Previous congresses have been established to disseminate information about nutritional therapy to improve the metabolic and nutritional disorders associated with chronic renal failure, both in patients who are not treated with dialysis and in those who are undergoing maintenance dialysis therapy. Knowledge in this area having expanded rapidly, the congresses have been designed so that clinicians and researchers pursuing basic and clinical investigations in various countries could meet and discuss areas of mutual interest and concern. The Organizing Committee of the Third Congress was composed of individuals from the United States, France, the Federal Republic of Germany, and Italy. Topics addressed included muscle and cellular metabolism in renal failure, catabolic stress in renal failure, endocrinometabolic disorders in acute and chronic renal failure, nutritional and metabolic aspects of continuous ambulatory peritoneal dialysis, conservative management of chronic renal failure, techniques for prevention of progression of chronic renal failure, nutritional management of pediatric patients with renal failure, and the role of sodium and potassium intake in the etiology and management of hypertension.

The Institute supported a colloquium entitled "Advances in Diabetes Epidemiology," which was held near Paris, France, in May 1982. Additional funding was provided by INSERM. The colloquium was particularly timely because of recent

efforts to establish uniform diagnostic criteria for diabetes. These criteria have been adopted by several organizations concerned with the disease. A second development that made the colloquium so relevant was the advent of population-based registries. The meeting was an attempt to pool data from all over the world in light of considerable new information on the role of viruses, autoimmunity factors, and histocompatibility antigens in the etiology and pathogenesis of diabetes. Also discussed were heterogeneity in each of the types of diabetes, genetics, environmental etiologies of insulin-dependent diabetes, and studies of blood glucose levels in different groups and populations.

The colloquium was held under the auspices of staff members of the Unité de Recherches Statistiques and other French institutions. In addition, there was a scientific committee composed of members from Australia, the Federal Republic of Germany, and the United Kingdom,

The NIADDK provided grants for a number of American scientists to attend the Twelfth International Congress in Perth, Australia, which was held in August 1982. Among the many topics covered were enzymology, enzyme mechanisms, protein synthesis, and the relationship between structure and function of biologically relevant molecules. Of high scientific quality, these triennial congresses of biochemistry play an important role in the progress of biochemical research throughout the world.

### **Intramural Programs and Activities**

Intramural scientists at the NIADDK engage in a broad range of collaborative activities, both in foreign laboratories and with scientists from other countries who make use of the resources at the NIH.

One program in which a number of intramural scientists participate is actually an initiative of governmental education authorities in Italy. It involves both travel to the NIH by young Italian scientists and corresponding visits to sponsoring Italian laboratories by NIADDK staff.

At NIADDK, one laboratory carrying on collaborative work under this program has been the Biochemistry of Cell Regulation Section in the Laboratory of Biochemical Pharmacology. Studies have been pursued on the structural properties of the receptor for thyroid stimulating hormone on normal thyroid plasma membranes, on plasma membranes of human and experimental thyroid tumors, and in strains of differentiated thyroid cells grown *in vitro*. These studies have established the role of glycoproteins and glycolipids in receptor recognition, the mechanism of message transmission, and the relevance of their functional expression in normal and disease states such as goiter, Graves' disease, and hyperthyroidism.



Research on vesicles coated with clathrin, a protein that provides a mechanism to bring thyroglobulin and other substances into the cell, is being done by an NIADDK clinical endocrinologist at the University of Naples.

A Fogarty Scholar-in-Residence from Japan is one of the two or three preeminent scientists involved in the chemical synthesis of peptides and proteins. Thus far, he has spent about 6 months in residence at the NIH, acting as a consultant to the Laboratory of Chemical Biology (LCB). He has been involved in work with NIH intramural scientists on the chemical synthesis of interferon and on the synthesis of peptides as inhibitors of the gelatin of sickle hemoglobin. During this time, the group synthesized and studied a number of peptides and tested their efficacy as gelatin inhibitors.

Additional collaborative study of synthetic peptide inhibitors of sickle hemoglobin gelatin is ongoing between LCB scientists and a Nobel Laureate at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. Using synthetic peptides synthesized at the NIADDK lab, scientists are studying the binding of several synthetic peptides to crystals of hemoglobin to try to establish the mechanism of their gelation inhibition. Once this information is available, LCB scientists will design new and probably longer peptides, with the assistance of the molecular graphics system of the NIH Division of Computer Research and Technology.

In a collaborative project with the Department of Morphology at the University of Geneva, Switzerland, the morphologic aspects of polypeptide hormone interaction with target cells of insulin action, particularly in the liver, are being studied. These are the first studies to combine a biochemical approach and a physiologic approach with morphologic probes to demonstrate surface interactions and intracellular processing of polypeptides.

Recent collaboration between the Nuclear Magnetic Resonance Section of the Laboratory of Chemical Physics and the Indian Institute of Science in Bangalore has centered on the basic

molecular structure of peptides, using various methods of spectroscopy and X-ray diffraction.

Another collaborative project involves the Laboratory of Biochemistry and Metabolism and the Weizmann Institute of Science in Rehovot, Israel. An effort is being made to map the three-dimensional structure of integral membrane proteins, using spectroscopic techniques. Integral membrane proteins, found in the phospholipid bilayer of cells, actually perform most of the active functions of the cell membrane. Researchers have collaborated to study, among others, bacterial rhodopsin, which is a unique pigment that permits bacteria to use light to generate energy (through the "proton pump" mechanism). The investigators believe that finding a way to inhibit the proton pump process may enable us to inhibit viral interaction with cells because the proton pump is always involved in such interactions.

### **The NIH Visiting Program and Health Scientist Exchange Program**

Under the NIH Visiting Program, scientists at the NIADDK sponsor investigators from many countries to pursue work in laboratories on the NIH campus, and in turn many NIADDK researchers visit and collaborate in laboratories and clinics abroad. As the inevitable result of such a program, the cross-fertilization of ideas has mutual benefits for the United States and the foreign countries involved. Often it can lead to new advances in biomedical research. The following countries were represented in the Visiting Program during 1982: Australia, Austria, Bangladesh, Belgium, Canada, China, the Federal Republic of Germany, France, Ghana, Greece, Hungary, India, Israel, Italy, Japan, Korea, Mexico, the Netherlands, New Zealand, Nigeria, Pakistan, Poland, Portugal, the Republic of South Africa, Spain, Sweden, Switzerland, Trinidad, the United Kingdom, Yugoslavia, and Zimbabwe.

# Chapter VII

## National Library of Medicine

### Introduction

The international programs of the National Library of Medicine (NLM) are a natural extension of NLM's domestic responsibilities. Cooperative in nature, these activities have relevance to both the developed and the developing world.

The advancement of biomedical and health research, education, and health care depends upon effective biomedical and health communications. Through its activities, products, and services, the NLM fills the important role of coordinating biomedical and health information as it collects, organizes, and disseminates this information not only domestically but also globally. The U.S. health professional benefits from the international character of the NLM collection, its data bases, and its functions; the world health community derives benefit not only from NLM's products but also from NLM's international collaborative undertakings.

NLM's international activities fall into six general categories: literature exchange, library services, Special Foreign Currency (P.L. 480) Program, MEDLARS cooperation, technical consultation, and participation in international organizations. Involving primarily a sharing of time, talent, and resources, these activities require a variety of mechanisms for execution, but all have a common objective: to benefit the U. S. health effort.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

##### International MEDLARS Agreement

NLM's international MEDLARS quid pro quo arrangements have been in existence since the first arrangements with the United Kingdom and Sweden in 1968.

There is no transfer of monies between the participating country and the NLM. The NLM makes available the MEDLARS system, technical documentation, and training either through tapes or online access to the NLM computer. The

participating country must meet technical criteria involving personnel, equipment, and fiscal resources and have a user community large enough to justify an extensive computerized service. The participating country then provides and/or funds the indexing of journal articles for input to the MEDLARS data base in return for access to the system. This practice is consistent with a policy adopted in 1966 by the Federal Council for Science and Technology, which was that Federal information systems would be made available in return for some contribution.

The NLM does not select the institutions that will serve as MEDLARS Centers. The country itself makes that choice after meeting certain technical criteria established by the NLM. The MEDLARS Center may be in an organization primarily concerned with medicine or health, in a library, or within an organization broadly concerned with science and technology. In all cases, the foreign MEDLARS Centers function as a national biomedical information resource.

A country has a choice of alternative MEDLARS arrangements: it may operate the system on its own computer using the NLM tapes (with or without NLM software) or it may use telecommunications linkages to access the NLM computer. Table 7-1 lists the regions, organizations, and modes of access.

The Karolinska Institutet of Sweden hosted a meeting of policy officials from each of the countries with MEDLARS Centers. The meeting included a description from each of the officials about recent developments, plans for the future, quid pro quo arrangements, the role of government in providing biomedical information, the impact of technology, and the relationship between developed and developing countries.

In their discussions of the role of the government, the members of the International MEDLARS Policy Advisory Group, which represents health-related scientific and educational institutions and libraries in 12 countries, prepared a statement recognizing the NLM's leadership role and affirming that biomedical and health information is basic to maintaining and advancing biomedical and health research, education, and care.

The Advisory Group's statement emphasizes the value of the MEDLARS system, referring to it as a national and international resource that



Table 7-1.--National Library of Medicine non-U.S. MEDLARS Centers

Region	Organization	Mode of Access to MEDLARS
Australia	The National Library of Australia (NLA)	Tapes/ Software
Canada	Canada Institute for Scientific and Technical Information National Research Council of Canada	Online NLM
Colombia	FUNDACION OFA and FONDO COLOMBIANO de INVESTIGACIONES CIENTIFICAS (COLCIENCIAS)	Online NLM
France	Institut National de la Sante et de la Recherche Medicale (INSERM) Ministere de la Sante Publique et de la Securite Sociale	Online NLM
Germany (Federal Republic)	Deutsches Institut fur Medizinische Dokumentation und Information (DIMDI) Der Bundesminister fur Jugend, Familie und Gesundheit	Tapes
Italy	Istituto superiore di Sanita Ministero della Sanita	Online NLM
Japan	Japan Information Center of Science and Technology (JICST) Science and Technology Agency	Tapes
Mexico	Centro Nacional de Informacion y Documentacion en Salud Ministerio de Salud	Online NLM
South Africa	Institute for Medical Literature South African Medical Research Council	Online NLM
Sweden	Karolinska Institutet	Tapes/ Software
Switzerland	Schweizerische Akademie der Medizinischen Wissenschaften	Tapes
United Kingdom	The British Library	Online NLM
Intergovernmental Health Organization	Biblioteca Regional de Medicina (BIREME) Pan American Health Organization	Tapes/ Software

assists and enhances medical research, education, and health care delivery throughout the world. The statement describes the MEDLARS group of information services as an integral part of the research cycle and an important support to U.S. international relationships based on sharing knowledge, expertise, and facilities through bilateral arrangements. MEDLARS makes it possible to disseminate medical information efficiently and effectively to all countries, including those of the developing world.

#### Special Foreign Currency Program

The Library's Special Foreign Currency Program, authorized by P.L. 83-480, as amended, relies upon appropriations of U.S.-owned, local foreign currencies to make awards for scientific writing and publication projects in cooperating countries, including Egypt, India, Israel, Pakistan, Poland, and Yugoslavia. The programs in Israel and Poland were continued under collaborative bilateral research agreements.

Projects in the six cooperating countries include preparation of critical reviews and monographs analyzing biomedical research and practice; translations of foreign monographs in the health sciences; studies in the history of medicine; publication of major international symposia and conference proceedings; and preparation and publication of bibliographies, guides, and other literature tools in the biomedical sciences. The program enables the NLM to draw on foreign scientific personnel and resources in obtaining and disseminating information important to U.S. health educators, practitioners, and researchers.

The projects are multiyear, and during FY 1982 89 studies were active. Over 50 percent of the current program is carried out in Poland and Egypt, with about 20 percent in India. New critical reviews and monographs in health fields constitute 45 percent of the projects, with projects concerned with the history of medicine representing another 30 percent.

Among the new P.L. 480 projects activated in FY 1982 were a critical review on the endocrine system in patients with acute renal failure, publication in Egypt of the seventh volume of a major international bibliography of ticks and tickborne diseases, and translation of a Russian study of the geographical pathology of atherosclerosis. Among the publications received in FY 1982 resulting from prior support was a monograph entitled Chronic Hemodialysis as a Way of Life, written by two internationally renowned experts and addressed to medical and psychiatric practitioners. The book covers every aspect of hemodialysis. Another study recently published with support from the P.L. 480 Program was an English language translation of the last work of the late Alexander R. Luria, a widely recognized Soviet neuropsychologist; the book, translated in India and printed in the United States, is called Language and Cognition. Among the recently published studies in the history of medicine was Two Great Scientists of the Nineteenth Century: Correspondence of Emil Du Bois-Reymond and Carl Ludwig. This book presents a 50-year correspondence between two of the most important figures in the development of modern physiology and offers an insight into 19th-century medicine. The text was translated in Tunisia and printed in India.

## Activities With International Agencies

### World Health Organization

The NLM and the WHO Special Program for Research and Training in Tropical Diseases continued to cooperate in the publication of the Quarterly Bibliography of Major Tropical Diseases. The NLM prepares camera-ready copy that WHO prints and distributes to approximately 5,500 institutions in the developing countries. The bibliography is prepared from the

MEDLINE system and covers those diseases WHO had identified for special attention--filariasis, leishmaniasis, leprosy, malaria, schistosomiasis, and trypanosomiasis.

Furthermore, the WHO Program for Control of Diarrheal Diseases requested NLM's assistance in a Bibliography of Acute Diarrheal Diseases which is planned for periodic publication. This bibliography has been issued for the first time within this fiscal year following the same procedure of NLM's production of camera-ready copy from MEDLINE and WHO's printing and distribution.

The NLM and WHO continued the collaborative arrangement for provision of photocopy of journal articles to developing countries of the WHO regions of Africa, Eastern Mediterranean, and Southeast Asia. Under this arrangement, WHO supports one individual in residence at the NLM to provide this service. This modest level of activity responds only partially to the existing biomedical and health information needs of developing countries.

WHO has been actively working with developing countries to identify existing resources for biomedical and health information and to develop mechanisms for providing information services. The Director of the National Library of Medicine is a member of the WHO Advisory Committee on Medical Research Subcommittee on Biomedical Information. Included in the summary and recommendations of the final 1982 report of the subcommittee was the following observation:

Regional and national medical libraries and information networks to share scarce resources are now being planned or are under implementation or development in all regions in close contact with Headquarters. Those efforts are to be expanded and sustained as they are a prerequisite for the successful implementation of WHO health plans. The model of resource sharing and network implementation that is being developed by BIREME should be examined for its potential application in other areas of the world.

The Subcommittee is pleased that several regions have or are preparing regional Index Medicus, that PAHO and Headquarters have developed document information services using the "Medical Subject Headings" (MeSH) vocabulary, and that SEARO and Headquarters are planning a pilot project for the bibliographic control of fugitive health literature on health services research.

The Subcommittee recognizes that there exist national literature, documents, audiovisual materials, etc., which are not now accessible in an organized manner.... Efforts to collect, organize and index such [fugitive] material into bibliographic systems should use the same internationally accepted cataloguing



rules and standards and MeSH, . . . resulting in bibliographic systems and products in the whole health field [which] will be compatible with each other and with the regional and global Index Medicus/MEDLARS.

The Subcommittee considers the selective dissemination of bibliographic information with abstracts as exemplified by the Quarterly Bibliography of Major Tropical Diseases as an important and cost-effective method to keep health researchers in developing countries informed about progress in their field of interest. Access to full articles should be improved by resource sharing networks, regional interlibrary loans (photocopies) services and library manpower training.

#### **Pan American Health Organization**

The NLM continues to work with PAHO and especially with the PAHO Regional Library of Medicine (BIREME) in Sao Paulo, Brazil.

The Library's Assistant Director for International Programs, a member of the Scientific Advisory Committee for BIREME, will participate in the 1983 meeting of this committee. BIREME is unique in the world as a regional resource. It provides library services and computer-based bibliographic services from the subset of the MEDLINE data base, trains Latin American librarians, and has produced a Latin American Index Medicus.

#### **International Council of Scientific Unions**

##### **Abstracting Board**

The Assistant Director for International Programs and the Deputy Director, as the NLM representative and alternate, respectively, to the International Council of Scientific Unions Abstracting Board, attended the annual meeting of the board. The board consists of information organizations from a number of countries. Topics discussed included collaborative undertakings, status of document delivery in various regions including the proposals of the Commission of the European Communities, working groups in various subjects, copyright, and an examination of the future role of the board in international, scientific, and technical activities.

##### **Visitors and Specialized Training**

The NLM continues to receive international visitors, as well as specialized delegations, who represented approximately 84 countries during FY 1982. Formal delegations were concerned with international communications, library management and resources, information systems management, and the impact of technology.

# Chapter VIII

## National Institute on Aging

### Introduction

By the end of the century, the total number of people in the world aged 60 and over will have doubled. Between 1975 and 2000, the number of aged in industrialized nations will increase 39 percent; for developing countries, the increase in this population will be 100 percent.

Although aging in itself is not a disease, the infirmities that accompany it must be examined and understood in order to extend the healthy and productive years, not simply to extend life itself. Although the relatively new fields of gerontology and geriatrics are developing rapidly, substantive collaboration across borders and seas is just beginning to emerge.

In May 1974, the United States National Institute on Aging (NIA) was created to support and conduct biomedical, social, and behavioral research and training related to the aging process and to the diseases and other special problems of the aged. The Institute has extended its influence beyond national boundaries, demonstrating an interest in collaborating with the international scientific community and with multinational organizations, as reported in the sections that follow.

### Summary of International Programs and Activities

#### Activities With the World Health Organization

NIA's association with WHO began during the initial years of the Institute's existence. The relationship was formalized in 1980 when the NIA was designated as the first WHO Collaborating Center for Joint Cooperation on Research on the Care of the Aged. Over the years, the NIA Director and other staff members have served as advisors to the WHO Global Program on the Care of the Aged. During FY 1982, members of the Institute's staff have participated in a number of WHO-sponsored events.

In October 1981, the NIA Director took part in a presentation titled "Research in Gerontology" before the WHO Global Advisory Committee on Medical Research (GACMR). On the basis of that meeting the committee recommended that a WHO group be convened to plan future cross-

national epidemiological and social-survey research on the elderly and that a second WHO group be established to develop a program on senile dementia, because "a concentration of ideas, techniques, and research workers" now exists, as observed by the GACMR. The Group on Senile Dementia met in April 1982 and proposed seven areas of research for consideration: points of possible intervention in neurosynaptic transmission and neuropeptides; low viruses and prions; genetic susceptibility; autoimmunity; trace metals; noninvasive studies of cerebral metabolism, including positron emission tomography; and neural membrane studies. The Institute will meet in January 1983. In both instances, the WHO Global Program on Care of the Aged is expected to develop worldwide networks of collaborating institutions.

Also in connection with this meeting, the NIA updated an analysis of participating institutes and various national programs to provide a better understanding of their goals, priorities, organizational structures, and activities. Overall, the analysis reveals that nations with widely differing political, cultural, economic, and social settings recognize the need for gerontologically related research and that this recognition often is in response to the growing number of older people in their own population. The WHO has viewed this effort as a basis for collegiate collaboration between the institutes described in the profiles. The network is open-ended, and other institutes are welcome to take initiatives for research collaboration, either collectively with the network or individually with an institute. Copies of "Profiles of National Research Institutes and Programs on Aging" are being transmitted by WHO to organizations concerned with aging listed in United Nations documents and by the International Federation on Aging to all its national member organizations. Interested individuals may obtain a copy from the International Coordinator, National Institute on Aging, Building 31, Room 2C07, National Institutes of Health, Bethesda, Maryland 20205.

#### Extramural Programs

The Institute's Biomedical Research and Clinical Medicine Program currently supports basic and clinical research through grants to five



investigators outside the United States (in Canada, Belgium, and Israel). Three of the projects deal with molecular and cellular biology, one with immunology, and one with the clinical pathology of Alzheimer's disease.

The project on Alzheimer's disease is being conducted by an investigator at the University of Western Ontario. It is designed to determine the relationship between pathological and clinical measurements of Alzheimer's disease using clinical, neurophysiological, biochemical, histopathological, and radiographic characteristics of a well-defined clinical population. Results obtained during the first year of the grant indicate that viable synaptosomes (preparations of presynaptic nerve endings) suitable for neurochemical or neuropharmacological studies can be prepared if brain tissue is obtained within approximately 8 hours after death. The synaptosomes will be used to provide data related to the disease process in patients afflicted with Alzheimer's disease, particularly with regard to neurotransmitter function.

Although the Behavioral Sciences Research Program of the Institute does not support investigators from outside the United States directly, it does support six domestic grants with foreign components. These are primarily cross-cultural and cross-national comparative studies related to such areas as aging and support systems, community influence, retirement levels, and economic analyses involving specific populations such as those found in Hong Kong, the U.S.S.R., Israel, and Eastern European countries.

### **International Conferences, Seminars, and Meetings**

The United Nations World Assembly on Aging (UNWAA) was held at the Hofberg Palace in Vienna, Austria, from July 26 to August 6, 1982. It was convened to address issues pertaining to worldwide population changes caused by declining mortality, fertility, and migration. Numerous preparatory meetings, beginning as early as 1979, were held around the world.

The NIA contributed to the assembly in two capacities--as a member of the United States Federal Interagency Committee on Aging for the UNWAA and as a WHO collaborator. The NIA Director participated in the assembly as an advisor to the WHO delegation. WHO, as a specialized agency of the United Nations, presented a "Technical Discussion Paper on the Health Policy Aspects of Aging," which was largely derived from the NIA-supported WHO Preparatory Conference for the UNWAA held in Mexico City in December 1980.

Health and nutrition were dominant issues in the assembly's International Plan of Action, a plan that gives high priority to research on the developmental and humanitarian aspects of

aging. Of the 40 national reports submitted, the NIA provided the section on Research and Training of the U.S. National Report.

The developing countries' recognition that they will experience dramatic changes in age composition was a primary achievement of the assembly. The International Plan of Action calls for the Center for Social Development and Humanitarian Affairs in Vienna to serve as the U.N. focal point and coordinator for aging and to follow up on the objectives of the UNWAA.

Other international workshops and conferences in which Institute staff participated during FY 1982 are listed below.

- WHO Workshop on Information Transfer in Mental Health
- Planning Meeting for the WHO Conference on Self-Care/Health Promotion Among the Elderly (to be held in 1983)
- WHO Workshop on Health Planning for the Elderly
- Special Meeting of the National Academy of Medicine of Mexico Concerning the Needs of the Elderly
- International Congress on Aging and Environmental Factors
- International Conference on Life-Course Research on Human Development
- European Society of Neurochemistry
- International Congress on Neuropathology
- Fifth International Symposium on Cardiology and Aging
- Third International Erwin Riesch Symposium on Cardiac Adaptation to Hemodynamic Overload Training and Stress
- Tenth International Meeting of the International Society for Social Gerontology
- Chemical Institute of Canada's 65th Canadian Chemical Conference and Exhibition
- Thirteenth Collegium Internationale Neuro-Psychopharmacologicum Congress
- Meeting in France to Consult on Policies Concerning Research and Aging in France
- WHO/Serono Symposia on Role of Basic and Applied Research in Achieving Health for All by the Year 2000

- International Conference on Aging of the Brain
- Tenth Aharon Katz-Katchalsky Conference
- Meeting with the WHO Collaborating Center on Health and Psychosocial Factors
- International Symposium on the Aging Brain

### **Intramural Programs and Activities**

The majority of the Institute's intramural research on aging is conducted at the Gerontology Research Center in Baltimore, Maryland. In FY 1982, information and research results were exchanged with visitors from 13 countries: Australia, Brazil, Canada, China, the Democratic Republic of Germany, France, the United Kingdom, Italy, Japan, Sweden, Switzerland, Thailand, and Yugoslavia.

The Human Performance Section of the Clinical Physiology Branch has two projects involving scientific exchange at the international level. Sample populations of normal Guamanians (Chamorros) and of Guamanians afflicted with amyotrophic lateral sclerosis/Parkinsonism dementia complex are utilized in collaboration with Japan for cross-sectional and longitudinal evaluation of bone loss in a study related to osteoarthritis and bone loss, which are age-related changes of the human skeleton that may result in incapacity.

The second study on normal human variance involves a continuing collaborative effort with WHO and other national and international biological laboratories located in France, New Guinea, Greece, New Zealand, India, and Australia for the purpose of coordinating the col-

lection, evaluation, and interpretation of dermatoglyphic data. The objectives of this project include the study of dermatoglyphics as it relates to aging, to distribution among human populations, and to genetics; and as it functions as a disease marker.

Thus far, the study has revealed significant differences in the digital pattern frequencies of patients with breast cancer, individuals with high risk for developing breast cancer, and non-affected controls.

### **NIH Visiting Program and Health Scientist Exchange Programs**

The NIA intramural program continues to enjoy active Visiting Program participation. During FY 1982, 34 scientists from 16 countries--Australia, Canada, Chile, Egypt, Finland, France, Hungary, India, Israel, Italy, Japan, Poland, Sri Lanka, Sweden, Turkey, and the U.S.S.R.--received research training in the laboratories at the NIA Gerontology Research Center in Baltimore.

The areas of research in which guest workers participated include pathophysiological and hormonal regulation of membrane transport systems; alteration of kidney membrane-bound enzymes in aging rats; studies on the relationships of cerebral metabolism to brain function and aging, the blood-brain barrier and central nervous system function, and transport systems active at the blood-brain barrier; drugs potentially useful for diseases prominent in senescence; the role of cell membrane structure on cellular recognition; a survey of the immune function of participants in the Baltimore Longitudinal Study of Aging; and learned modification of visceral function in man. In summary, Visiting Program participants contributed to 16 of 60 NIA intramural projects.



# Chapter IX

## National Institute of Allergy and Infectious Diseases

### Introduction

The National Institute of Allergy and Infectious Diseases (NIAID) was formally established by law in 1948 as the National Microbiological Institute. Its name change in 1955 reflects a heightened emphasis on research in communicable diseases and immunological disorders. The NIAID assumed primary responsibility for activities in tropical medicine at the NIH in 1968 when the NIH Office of International Research was disbanded. In 1979, the Office of Recombinant DNA Activities was assigned to the NIAID.

Approximately 600 staff members at Bethesda, Maryland, and at the Rocky Mountain facilities in Hamilton, Montana, carry out NIAID intramural research while the extramural research program is implemented through research or training grants and contracts awarded to academic and research institutions. In FY 1982, tropical medicine and international research accounted for 73 percent of the extramural budget.

In industrialized societies patients seek medical attention for infectious diseases more frequently than for any other disorder. In developing countries, these diseases are the leading cause of reported morbidity and mortality. Thus, advances in the domestic NIAID program have inherent and far-reaching relevance for national health authorities outside the United States and for agencies that cooperate with them in applying new knowledge and technology to disease prevention and control.

During FY 1982 the NIAID continued to assign special priority in its Tropical Medicine Program to filariasis, leishmaniasis, leprosy, malaria, schistosomiasis, and trypanosomiasis--the six diseases targeted for intensive research by the World Bank/UNDP/WHO Special Program for Research and Training in Tropical Disease (TDR). Priority placement on the six diseases also occurs through the NIAID International Cooperation in Infectious Diseases Research (ICIDR) Programs and through the Tropical Disease Research Units (TDRU's). Research progress on each of these tropical diseases is reported separately to facilitate communication and coordination with WHO and other international agencies that constitute a global network on research in tropical diseases.

The NIAID Tropical Medicine Program also addresses other issues for which international collaboration is essential to complement the domestic research effort, including general parasitology; tropical bacteriology, mycology, and virology; rickettsioses; and vector pathogens. Infectious diseases that constitute more serious public health problems in developing countries than in the United States are not included in NIAID's reporting of its Tropical Medicine Program because the majority of these conditions are covered in NIAID domestic programs. Examples include gastroenteritis other than cholera, hepatitis, acute respiratory illnesses, and sexually transmitted diseases. Thus, in addition to the NIAID Tropical Medicine Program, the bulk of which is carried out in the United States, this report also summarizes NIAID international activities in all disease areas.

General parasitology consists of research on parasites of importance to human health other than those covered by the TDR Program. Included are awards for basic research projects, parasitology research training, and career development awards that are not easily categorized specifically for any one of the targeted TDR diseases. The NIAID regards basic research in parasitology as a prerequisite to further advancements in the prevention or control of all six parasitic diseases of TDR. Indeed, the PHS, Army, Navy, U.S. Agency for International Development (USAID), and WHO disease-oriented initiatives have evolved from breakthroughs in basic research and will continue to rely on them to achieve their goals of vaccine and drug development or vector control.

The rickettsial program, representing 6 percent of NIAID activity, is directed primarily toward Rocky Mountain spotted fever. Tropical bacteriology awards (7 percent) focus on cholera and related organisms, tuberculosis and mycobacteria other than leprosy, and, to a lesser degree, spirochetes, plague, and yersinia. Although WHO has recently established a global Diarrheal Diseases Control Program with a major research component in epidemiology, improved drugs, and vaccine development, NIAID activities in viral and bacterial diarrheas (other than cholera), as indicated, are included in the regular program and hence are not part of the Tropical Medicine Program. Histoplasmosis and coccidioidomycosis

research (1.4 percent) constitutes the bulk of activities in tropical mycology.

Tropical virology (7.4 percent) concentrates research projects on arboviruses, rabies, and other viral agents of public health importance (e.g., Lassa fever) that are not endemic to the United States. Vector pathogen activities (6.3 percent), by contrast, consisted of 26 projects, 10 on mosquito studies and others on tick, mite, and snail vectors of human viral, rickettsial, and trematode diseases.

The three major categories of NIAID support for Tropical Medicine and International Health are intramural research, domestic extramural research, and competing foreign awards. Foreign investigators are eligible to compete with U.S. investigators for NIAID grants and, under special conditions, for contract funds. Most NIAID-sponsored international research, however, is generated through NIH awards to U.S.-based scientists and institutions. Approximately 70 percent of the awards are for extramural grants or contracts to U.S. investigators or institutions. Awards to non-U.S. scientists or institutions represent 3 percent of the total Tropical Medicine and International Research budget.

NIAID grants for ICIDR are intended to provide linkages for research conducted outside the United States. The ICIDR Program, as well as the NIAID-supported Tropical Disease Research Units within the United States, is discussed in more detail under bilateral activities. Additional award mechanisms include bilateral medical research programs and the Special Foreign Currency (P.L. 480) Program, which involves six countries and is coordinated by the Fogarty International Center for the NIH. In FY 1982 the NIAID was most actively involved with Argentina, Australia, Brazil, China, Colombia, Costa Rica, the Dominican Republic, Egypt, France, Gambia, Ghana, India, Indonesia, Israel, Japan, Kuwait, Mexico, the Netherlands, Nigeria, Pakistan, Panama, Poland, Sierra Leone, Sudan, Sweden, Switzerland, Thailand, Trinidad and Tobago, the United Kingdom, and Venezuela.

Going beyond the major award categories described above, the full extent of NIAID support for international health includes the overseas components of intramural or domestic extramural awards outside the diseases classified under the rubric of tropical medicine.

## Summary of International Programs and Activities

### Bilateral Agreements and Other Country-to-Country Activities

The NIAID conducts scientific exchange and collaborative research through a variety of

mechanisms that extend from informal direct contact between investigators to formal agreements for cooperation between the United States and other governments. Because of its research responsibilities in tropical diseases, microbiology, and vaccine development, the NIAID has a particular need to foster cooperation with scientists and institutions in developing countries. In recent years, formal bilateral science and technology agreements with developing countries have proliferated, encouraging a tendency for these bilateral programs to move into additional areas such as immunology and genetic engineering.

#### Argentina

Long-standing collaboration with the Instituto Fatale Chaban (Buenos Aires) on the cell biology of *Trypanosoma cruzi* strains and single cell isolate clones has been maintained.

#### Australia

Formal collaboration was begun between the NIAID and the Fairfield Hospital (Melbourne) on the biology of the hepatitis A virus. Collaboration was also initiated between the NIAID and the Australian National University. Research here will focus on the biology of mousepox virus and development of a simple, sensitive, and specific *in vitro* test for ectromelia virus to control and prevent this disease, which has recently produced epizootics at the NIH and represents a serious threat to U.S. biomedical research.

At present the NIAID extramural program supports five Australian investigators at the Walter and Eliza Hall Institute of Medical Research (Melbourne). In addition to ongoing support for research on mechanisms of lymphocyte-antigen interactions, recent awards support the use of animal models for the development of vaccines against parasites, cell surface monitoring by recirculating lymphocytes, investigation of T cell development in the thymus, and analysis of T hybridomas with defined idiotypes.

#### Bangladesh

Collaborative research in Bangladesh has focused on the Cholera Research Laboratory (CRL) in Dhaka. This productive relationship is chronicled in Cholera: The American Scientific Encounter by Seal and van Heyningan, which will be published in early 1983. The NIAID collaborates with the International Center for Diarrheal Disease Research/Bangladesh (ICDDR/B) for longitudinal studies of viral gastroenteritis in infants and young children. (This research laboratory was designated as the ICDDR/B in 1978 and functions as a multilateral research institute.) NIAID awardees in enteric diseases at



Harvard, Johns Hopkins, Maryland, and Washington Universities continue to collaborate with ICDDR/B. In February 1982, NIAID staff visited ICDDR/B to identify additional areas for scientific exchange and collaboration.

### Belgium

The NIAID continues collaboration with several Belgian scientists on the ontogeny and differentiation of cells of the rabbit immune system. The Director, Institut de Medicine Tropical (IMT) Prince Leopold (Antwerp), visited the NIAID early in 1982 to discuss development of a joint research effort directly between the NIAID and IMT, which would include joint activities in developing countries.

### Bolivia

The NIAID is exploring the possibility of collaborative activities in Chagas' disease and leishmaniasis with the Centro Nacional de Enfermedades Tropicales in Santa Cruz. Discussions were also held with the Institute of High Altitude Biology in La Paz on mutual interests related to effects of altitude and internal migration on patterns of communicable diseases.

### Brazil

Through a number of activities in Brazil, the NIAID has developed strong institutional ties. Efforts are now underway between the Fundacao Oswaldo Cruz (FIOCRUZ) and the NIAID to develop a joint work plan in tropical medicine.

In its intramural program, the NIAID has offered research training and bench facilities to Brazilian scientists for many years. Active collaboration continues with scientists at the University of Goias on the pathogenesis of leishmanial and *T. cruzi* infections. During FY 1982 an NIAID Visiting Scientist spent 8 months at the University of Boias in cooperation with WHO to study Chagas' disease. Four of the 10 ICIDR awards made in FY 1982 to U.S. investigators are for collaborative studies in Brazil. Cornell University Medical College collaborated with the University of Bahia on Chagas' disease and the endemic forms of cutaneous, mucocutaneous, and visceral leishmaniasis. The Harvard School of Public Health currently in its second ICIDR Program project, is collaborating with the University of Bahia and FIOCRUZ in Rio de Janeiro on Chagas' disease and schistosomiasis.

FIOCRUZ is also involved in a University of South Florida ICIDR exploratory grant on the spread of schistosomiasis in newly developed agricultural colonies in the northeast (Piaui) and in settlement areas along the Trans-Amazon Highway. Columbia University participates in collaborative research with the Federal University of Rio de Janeiro in which lectins are being

used to study cell surface carbohydrates of virulent and avirulent forms of *Leishmania*.

The Cornell on-site coordination for lab and field studies is based at the FIOCRUZ laboratory in Brotas, where major responsibility is building and maintaining a small animal colony. Most of the work at the FIOCRUZ is concerned with the immunology and biochemistry of leishmaniasis.

At the Professor Edgard Santos Hospital, Bahia University investigators are exploring the genetics and clinical aspects of American visceral leishmaniasis (AVL or kala-azar). Carefully designed, the genetic studies of AVL should yield definitive results on whether a genetic risk factor is associated with AVL. The immune studies are concerned with lymphocyte transformation, suppressor cell concentration, and T helper and B cell activity. Also in process are field studies in Jacobina on AVL, a prospective longitudinal field study of AVL that has already provided new insights into the natural history of the disease, and studies of cutaneous and mucocutaneous leishmaniasis in Tres Bracos.

At the Federal University of Bahia, the laboratory, which is managed by a Harvard immunoparasitologist who established the ELISA test for serological identification of Chagas' disease, U.S. and Brazilian collaborators are hoping to develop an ELISA test for detecting circulating *T. cruzi* antigen to circumvent xenodiagnosis, a cumbersome and slow diagnostic technique that requires weeks instead of hours for results. Monoclonals and their corresponding antibodies developed at Harvard will be used to identify strains of *T. cruzi* collected in different parts of Latin America.

The Professor Edgard Santos Hospital, which houses a cardiology unit directed by the ICIDR's Brazilian collaborator, is engaged in a classical study of Chagas' cardiomyopathy. Field studies on Chagas' disease are planned and coordinated by a Brazilian epidemiologist trained at Harvard. Entomological studies stemming from collaboration between the on-site coordinator and FIOCRUZ provide valuable information to control units working in the study area.

### Canada

NIAID scientists are collaborating with the University of Western Ontario on the genetic control and mapping of endogenous proviruses. During FY 1982, a new NIAID grant was awarded to the Montreal General Hospital for study of INR gene-complex probes in host-parasite interactions. A second award at the University of Manitoba concerns the suppression of the IgE response.

### China

The U.S.-P.R.C. Joint Committee on Science and Technology in Medicine and Public Health



held its first meeting in Beijing in June 1979. The NIAID was assigned lead responsibility for immunology and secondary responsibility with the Centers for Disease Control (CDC) in parasitology and infectious diseases. The parasitic and infectious diseases emphasized in the bilateral health protocol are malaria, schistosomiasis, hepatitis, and influenza. The NIAID subsequently assumed the lead role in recombinant DNA research within the Immunology Protocol.

As a result of the exchange visits of the U.S. and Chinese coordinators, the protocol for cooperation in immunology was modified for FY 1981-82 to include the immunology of infectious and parasitic diseases; cancer; diseases of the immune system, including primary immune deficiency diseases; autoimmunity and allergy; and skin and organ transplantation. The research approaches will involve immunobiology, immunogenetics, molecular immunology, immunopharmacology, and clinical immunology. The Immunology Work Plan provides for scientific exchange, research training, working groups, and collaborative research in immunogenetics and clinical immunology. The U.S.-P.R.C. Joint Committee endorsed these modifications at its second meeting in the fall of 1982. The third meeting is scheduled for FY 1983 in Bethesda.

By mutual consent, the highest priority in the Immunology Protocol is to enhance the research training opportunities for promising younger Chinese scientists at leading U.S. institutions. The Chinese Government, WHO, and private foundations have been very active in this area with U.S. universities outside the U.S.-P.R.C. Joint Committee and with minimal NIAID involvement. The Joint Committee has been an effective catalyst for research training and cooperative research at the NIH and other Federal agencies. In May 1982, U.S. scientists visited the University of Beijing and the Institute of Basic Medical Sciences, under the Immunology Protocol. An NIAID scientist was one of three U.S. scientists who participated in a workshop, "Biochemistry of Schistosomiasis," in Shanghai in September 1982; an NIAID grantee at the Academy of Natural Sciences (Philadelphia) traveled to China to study the distribution and ecology of snail vectors of schistosomiasis in Malaysia and Thailand.

In FY 1982 NIAID signed a 2-year interagency agreement with CDC to share costs on a collaborative protocol with the Institute of Virology (Beijing) and Shanghai First Medical College to study the efficacy of the NIH inactivated hepatitis B antigen (HBsAg) carrier mothers. Vaccines that were previously studied in Chinese adult volunteers are now being provided to infants born to HBsAg carrier mothers in Beijing and Shanghai.

The NIAID also supported the participation of U.S. scientists in a workshop entitled "Origin of Pandemic Influenza Viruses."

## Colombia

After 20 years of NIAID support for the International Center for Medical Research (ICMR) in Cali, scientists at Tulane University have proposed collaborative research with the Colombian Fund for Research (COLCIENCIAS) under the ICIDR mechanism. Now in its second year, the research emphasizes both epidemiological and basic biological investigations of selected vector-borne diseases, especially filariasis and trypanosomiasis. The ELISA test is being used for serological testing of patients from endemic areas with W. bancrofti. Strains of T. cruzi and T. rangeli have been cloned and will be reevaluated biologically and for isoenzyme characters prior to large-scale production of stage-specific antigens.

As the Tulane-COLCIENCIAS ICIDR builds on long-standing ICMR collaboration, joint publications in refereed journals are already beginning to appear. Field studies along the Colombian bank of the Amazon demonstrated an average prevalence of mansonellosis in teen-aged and adult Amerindians of 47 percent (range 16-85 percent). Entomological studies confirmed studies in Brazil that Simulium amazonicum and S. argentiscutum serve as intermediate vectors and confirmed conclusively for the first time in South America that culicine mosquitoes (C. insinuatus) can serve as vectors. Similar studies confirmed the presence of Dipetalonema pers-tans in the Colombian Amazon (Guainia) and that its prevalence (10.6 percent) and distribution may be far greater than previously suspected.

## Costa Rica

For 7 years, the NIAID has supported epidemiological studies of viral hepatitis by U.S. and Costa Rican scientists associated with Louisiana State University. In FY 1982, the team reported on a prospective investigation of the spread of hepatitis A virus (HAV) within households in two rural areas in Costa Rica. The initial prevalence of anti-HAV antibody was 26 percent in children and 71 percent in adults. Overall, 70-83 percent of antibody negative contacts acquired HAV infection. In contrast to observations in the United States, almost all "susceptible" adults developed inapparent infection while the clinical/silent case ratio in children was 1.8/1. The absence of IgM in older people suggests that antibody conversion in many Costa Rican adults represents reinfection and restimulation of IgG rather than new disease.

## Denmark

In October 1981, the Deputy Director General of the National Board of Health visited the NIAID.



## Dominican Republic

The University of Arizona collaborative studies between the NIAID and the Instituto Dermatologico (Santo Domingo) continue. The studies are significant because this focus on leishmaniasis in the Dominican Republic is the only documented concentrated attention on this disease in the Caribbean proper. This study has demonstrated a uniquely high incidence of diffuse cutaneous leishmaniasis, a rare manifestation previously reported in Ethiopia and Venezuela.

The University of South Florida is supported through the NIAID regular grants program to study filariasis in the Dominican Republic.

## Ecuador

In April 1982, the Chief, National Planning Division, Ministry of Public Health, visited the NIAID under the auspices of the Eisenhower Exchange Fellowship Program.

## Egypt

The NIAID has been involved in collaborative research with Egyptian investigators for more than a decade, most recently under the terms of the U.S.-Egypt Agreement for Collaboration in the Areas of Science and Technology. Collaborative projects funded by the Special Foreign Currency (P.L. 480) Program were the following: (1) Taxonomy of Genus *Bulinus*, (2) Bionomics of Anopheline Vectors of Malaria, (3) Ticks and Tickborne Diseases of the World, and (4) Epidemiology of Bancroftian Filariasis.

The NIAID is involved in collaborative efforts with CDC-administered P.L. 480 projects. The Laboratory of Infectious Diseases and the NIAID-funded Infectious Enteric Diseases Study Center at the University of Texas (Houston) provide virologic and bacterial support respectively to the Diarrheal Diseases Project at the Epidemiology Study Center in Bilbais.

The NIAID contract with the Research and Training Center on Vectors of Disease (Ain Shams University) to produce a study entitled "Epidemiology and Control of Vector-Borne Diseases in Egypt," a USAID-funded project administered by the NIAID, began in December 1981. Cooperating Egyptian institutions in FY 1982 included the Ministries of Health and Agriculture; El Azhar, Canal, and Cairo Universities; and the High Institute of Public Health (Alexandria). Participating U.S. institutions included NAMRU-3, Walter Reed Army Institute of Research, CDC, Cornell, Harvard, Michigan State, and Yale. The first year activities concentrated heavily on the development of research projects in Rift Valley fever, leishmaniasis, malaria, and medical entomology.

## Finland

In FY 1982 the NIAID extended its contract with the Central Public Health Laboratory to provide followup studies of children immunized with meningococcal type A vaccine from 1974 to 1978. The original contract resulted from a 1973 request from the Finnish National Board of Health for assistance in dealing with an epidemic of that disease. The new contract includes evaluation of the response to *Hemophilus influenzae*, type B vaccine administered as a control in the 1974 efficacy trials. The recently signed Memorandum of Understanding between the DHHS and the Ministry of Social Affairs and Health provides for the development and testing of vaccines. The DHHS has proposed that the director of the NIAID Microbiology and Infectious Diseases Program serve as the U.S. coordinator in this program area.

## France

During FY 1982 the NIAID continued its 21 years of support to a Nobel laureate for his work on skin grafts and surface leukocyte antigens. The Institut Pasteur began work on a new NIAID grant to study mechanisms of antigenic variation in *T. equiperdum*. NIAID intramural scientists also collaborated with this institute on genetic studies of immunoglobulins and other serum proteins, with the CNRS on the structure and activity of immunologically important cells and proteins, and with the Faculty of Medicine/Brest on tickborne disease agents. In FY 1982 the NIAID initiated collaborative work for basic studies on mycoplasmas and related wall-free prokaryotes. Collaboration was also begun with the Hospital Cochin (Paris) on the structure and function of endogenous murine C type viral products. In September 1982, the Director, NIAID, visited INSERM and the Institut Pasteur to discuss opportunities for more extended Franco-American collaboration in immunology, microbiology, epidemiology, and clinical investigation.

## Gambia

The NIAID and NCI initiated discussions this year with the Medical Research Laboratories (Banjul) on the feasibility of cooperative epidemiologic studies on the efficacy of hepatitis B vaccine in preventing disease, duration of immunity, and prevention of hepato cellular carcinoma. NIAID intramural scientists and New York University staff spent several weeks in Gambia under USAID and WHO support to conduct field trials on the application of radio-immunoassay, using hybridomas to *P. falciparum* in the determination of sporozoite infection rates in *Anopheles gambiae* mosquitoes, a significant development in malaria research.

## Democratic Republic of Germany

A new intramural project was initiated in collaboration with the Academy of Science (Jena) on the molecular and genetic analysis of plasmid-mediated properties among streptococci.

## Federal Republic of Germany

Collaboration between the NIAID and the University of Munich on the systemics and vector relationships of parasitic arthropods continued. Grant support was also provided to the Max Planck Institute for Biology on the polymorphism of the major histocompatibility complex.

## Ghana

During FY 1982, NIAID intramural staff made a short trip to the Onchocerciasis Hospital in Tamale, supported through P.L. 480 funds. A protocol was developed and arrangements made for a hospital researcher and an NIAID medical staff fellow to collaborate in Ghana under a TDR grant to initiate clinical and immunologic studies of the reactions (Mazzotti) that occur after treatment of patients with diethylcarbamazine.

## Haiti

The Tulane ICIDR Program continues its collaborative project on the epidemiology of filarial infection in Haiti, with the Institut Francais d'Haiti. In November 1981 the Association of Medical Microbiology Chairmen met in Port-au-Prince, providing NIAID senior staff an opportunity to meet with USAID country health staff.

## India

Since 1962 the NIAID has participated in collaborative research with Indian investigators, largely through P.L. 480 Program funding. In December 1981 the Indian-U.S. Working Group on Health of the Joint Science and Technology Committee met in New Delhi to review and re-define priority diseases for collaborative research. Mutually agreed-upon areas for emphasis were acute respiratory diseases, diarrheal diseases, filariasis, guinea worm, hepatitis, Japanese encephalitis, leprosy, malaria, recombinant DNA technology, rheumatic fever and sequelae, and tuberculosis. The NIAID reviewed the status of these activities with the Indian Council of Medical Research staff in New Delhi in March 1982 and in Washington later in the year with the Secretary of the Ministry of Health and Family Welfare.

In July 1982 President Reagan and Prime Minister Gandhi met in Washington and agreed to

establish a Joint Indo-U.S. Senior Scientific Panel to consider research areas of priority to both countries. Biomedical research on leprosy, immunology, and prevention of blindness were identified as the three program areas in health. This initiative will begin in FY 1983.

A new area of cooperation to which the ICMR gives high priority is acute respiratory diseases, which are major causes of morbidity and mortality in Indian children.

Collaboration continues among the NIAID, the Tuberculosis Research Center (Madras), and the Madras Medical College on the immunology of filarial infections and the pathogenesis of tropical eosinophilia and lymphangiitis. Current studies under the project include (1) evaluation of the pathogenetic significance of blocking antibodies that regulate immediate hypersensitivity responses in patients with filariasis, (2) determination of the mechanisms responsible for the control of allergic responses to the parasite, (3) comparison of the IgE regulatory mechanisms in patients with filariasis and other allergic disorders, (4) definition of the IgE as opposed to the IgG response of patients with filariasis to other specific antigens, (5) production of monoclonal antibodies to filarial antigens for use in the development of immunodiagnostic or protective immune reagents and, (6) chemotherapeutic studies of optimal drug regimens for this difficult-to-manage disease.

The NIAID continues collaborative studies at the National Institute of Virology (Poona) on the epidemiology of hepatitis in India. With the application of recently developed laboratory tests, it is now apparent that the 1955-56 massive water-associated outbreak of hepatitis in Delhi was neither hepatitis A nor B. Ongoing studies indicate that non-A, non-B hepatitis is a common source of epidemic and sporadic hepatitis in India. NIAID experiments at the NIH have produced hepatitis in chimpanzees following the inoculation of infectious Indian material but have not yet recovered and characterized the etiologic agent. As epidemic non-A, non-B hepatitis is particularly severe during pregnancy, efforts are now underway to develop a study with the National Institute of Virology on the epidemiology of hepatitis of pregnancy and childhood cirrhosis. During FY 1982 collaboration was extended to include the Postgraduate Institute of Medical Education and Research (Chandigarh) and investigators in Srinagar.

Agreement to undertake a new area of cooperation--in Japanese encephalitis--was reached in FY 1982. In 1981 the Government of India made a policy commitment to eliminate leprosy as a public health problem by the end of the century. Indo-U.S. collaboration in leprosy has been shared within the PHS among the National Center for Hansen's Disease in Carville, Louisiana; NIAID; and CDC. The Central Jalma Institute for Leprosy (Agra) was awarded one of



the first two ITDR Fellows for a year of research training in mycobacteria at the Tuberculosis Research Center of the Veterans Administration Medical Center (Long Beach). Approval was confirmed for a collaborative P.L. 480 project between scientists of Johns Hopkins University and the Foundation for Medical Research (Bombay) on the screening of drugs for activity against leprosy and the detection of drug resistance.

The University of Hawaii has an ICIDR exploratory award to collaborate with the Aligarh Muslim University on the in vitro cultivation of human malarial parasites isolated in India, the drug susceptibility of Plasmodium falciparum, and the culture of Indian P. vivax strains in vitro. NIAID intramural scientists visited the Central Drug Research Institute (Lucknow), and two collaborative protocols were completed: "The identification of immunogens and immunosuppressive molecules in primate malarial" and "Studies on immunity to the sexual stages of the malarial parasite."

Plans for a fixed-site Indo-U.S. Workshop on Recombinant DNA were modified in favor of a March visit by a team of four U.S. scientists led by the Deputy Director of the NIAID. The team became familiar with leading Indian scientists and institutions active in this area. Further activities and followup are expected to be incorporated into the new Indo-U.S. Senior Scientific Panel.

In rheumatic fever and streptococcal disease, efforts are underway between the University of Tennessee and the ICMR Streptococcal Typing Center (New Delhi) to study the epidemiology of group M streptococcal protein in India.

A collaborative project with the All India Institute of Medical Sciences (AIIMS) to adapt the radioimmunoassay (RIA) technique to the detection of secretory tuberculo-protein has been developed by two scientists (one, a Nobel laureate) at the Montefiore Medical Center (New York City). If successful, this effort should facilitate the definitive diagnosis of primary central nervous system and other extrapulmonary forms of tuberculosis within days rather than the weeks now required for the culture and identification of Mycobacterium tuberculosis. The AIIMS is also in a position to apply the RIA technique to other health problems and to serve as a national center in this field.

## Indonesia

Representatives of the National Institute for Health Research and Development (NIHRD) visited the NIAID in November 1981 to become familiar with the NIH. In September 1982 an NIAID scientist made a short site visit to the USAID-supported Health Training, Research, and Development Project to examine the biomedical research subproject of the NIHRD.

## Israel

The NIAID contract with the Kuvim Center for the Study of Infectious and Parasitic Diseases (Hebrew University) on the "Epidemiology and Control of Vector-Borne Diseases in Israel" began operations in December 1981. This USAID-funded project involves significant collaboration in medical entomology with Beersheva University of the Negev and focuses heavily on leishmaniasis research and field studies and on surveillance for leishmaniasis, Rift Valley fever, and malaria.

During FY 1982 the NIAID supported three ongoing investigator-initiated grant awards at the Weizmann Institute for research on bioenergetics and control of bacterial behavior at Hadassah University Hospital on new approaches to marrow and organ transplantation and at the Israel Institute of Technology on the differentiation and activity of mast cells in culture. Active collaboration exists between the NIAID and the Hadassah Medical Center on the characterization of surface IgG in the clones of a murine B cell lymphoma.

## Italy

A transmissible hepatitis agent, the delta agent appears to be defective in that it requires coinfection with hepatitis B virus for its own synthesis. The delta agent is endemic in Italy where it was discovered in 1977. An NIAID scientist is collaborating with Italian investigators on this unique virological phenomenon. A scientist in Rome also continues his collaboration with the NIAID on rabbit IgG allotypes.

## Japan

The NIAID is currently involved in two Japan-U.S. initiatives. The first is the U.S.-Japan Cooperative Medical Science Program (JCMSP), initiated in January 1965. Under the terms of this agreement, both countries have undertaken joint cooperative biomedical research in diseases of particular importance in Asia. Under P.L. 86-610 (the International Health Research Act of 1960) the State Department coordinates foreign relations and policy of the program while DHHS is responsible for the scientific elements. The NIAID has been the lead institute within the NIH and DHHS since 1968. Although the JCMSP operates as a bilateral program, scientists from other countries and/or international agencies often participate. Applications submitted within the context of this program by U.S. scientists compete for available funds on the basis of their scientific merit without a special NIAID budget set-aside. Japanese scientists, in contrast, depend on the program to facilitate their funding proposals.



Currently there are eight panels: leprosy, tuberculosis, cholera, hepatitis, parasitic diseases (schistosomiasis and filariasis), viral diseases (arboviruses, rabies, rotaviruses), environmental mutagenesis and carcinogenesis, and malnutrition. These panels meet annually either in the United States or Japan. The Director, NIAID, and staff members serve as the Secretariat to the U.S. delegation to the JCMSP and to six of the panels.

At the 1982 JCMSP Joint Committee meeting in Tokyo, the formal review of the Leprosy and Parasitic Diseases Panels was completed, and the Tuberculosis and Viral Diseases Panels were initiated. The committee recommended that the Leprosy and Parasitic Diseases Panels be continued and held additional discussions of the Leprosy, Tuberculosis, and Parasitic Diseases Panels. Recognizing the common scientific interests of the Leprosy and Tuberculosis Panels, the committee recommended that these two panels hold combined meetings beginning in FY 1984. The committee agreed also that the guidelines of the Parasitic Diseases Panel should be reviewed to accommodate new technologies and changing needs. Preparatory to such action, a symposium will be held in conjunction with the July 1983 Joint Committee Meeting in Bethesda. Experts will be invited to present current scientific reviews for such parasitic diseases as malaria, leishmaniasis, and trypanosomiasis, in addition to schistosomiasis and filariasis.

The second U.S.-Japan initiative developed when the President of the United States and the Prime Minister of Japan signed the Japan-U.S. Science and Technology Agreement for Non-Energy Cooperation in May 1980. This agreement is separate from, but coordinated with, the JCMSP. Within this second bilateral program the NIAID has lead responsibility for three program areas: immunization (vaccine development), recombinant DNA research, and antiviral agents. At the first meeting of the U.S.-Japan Program for Cooperation in Science and Technology (Tokyo, September 1981), both countries agreed to continue to develop recombinant DNA research activities within the "umbrella" Science and Technology Program. The technical aspects of vaccine development and antiviral agents, however, will remain with the appropriate JCMSP Panel, with the referral of matters requiring policy review and decisions to the U.S. Chairman of the Science and Technology Program.

JCMSP panel meetings during FY 1982 included the following: cholera, virology, hepatitis, immunology, tuberculosis, leprosy, and parasitology. Meetings held under the auspices of the U.S.-Japan Non-Energy Science and Technology Program were limited to a symposium entitled "The Introduction of DNA into Eukaryotic Cells" and a meeting of the Recombinant DNA Panel.

Outside the two formal bilateral programs, two NIAID intramural laboratories have ongoing collaboration with Japanese scientists. One is actively involved with the University of Tokyo in the fractionation of lymphoid cell subsets with lectins that specifically bind to cell surface glycan differentiation markers. The other, the Rocky Mountain facilities, also maintains collaboration with scientists at the National Institutes of Health (Tokyo) on tickborne disease agents. In addition, the NIAID supports one extramural award at St. Marianna University on genetic studies in the Aedes (Finlaya) togoi mosquito.

#### Kenya

During FY 1982 the NIAID initiated a domestic grant to Cornell University to study the longitudinal effect of treatment of Schistosoma hematobium on the nutritional status of school children. Parameters to be followed include physical fitness and urinary excretion of iron.

#### Kuwait

The Director of the Immunology, Allergic and Immunologic Diseases Program (IAIDP) continues to serve as a consultant to the Ministry of Public Health in the development of a national allergic disease program and the construction of an allergy research center.

#### Mexico

The University of Washington has an exploratory ICIDR award for work with the National Polytechnic Institute (Mexico City) on the serodiagnosis of subclinical leprosy. During the past year the surface protein of live M. leprae has been found to consist of five major subunits. A 36,000 dalton subunit common to M. leprae, M. leprae murium, and BCG may represent a shared antigen. The NIAID continues association and collaborative research that began over 10 years ago with Mexican scientists and the Center for the Study of Amebiasis (Mexico City). The NIAID also provided support for U.S. scientists to attend an International Symposium on Immunobiology of Infectious Disease. Approximately 200 Mexican immunologists participated in the symposium. The PHS subsequently convened a meeting at the NIAID to discuss cooperation between the United States and Mexico on research and training in communicable diseases. Economic conditions in Mexico, however, limited followup.

#### Netherlands

Two intramural laboratories have continuing collaborative research activities with counterparts in the Netherlands: one with the Netherlands Red Cross Blood Transfusion Service on the



mechanisms of immune recognition of viral antigens and the other with the Catholic University of the Netherlands on the taxonomy, ecology, and colonization of parasitic arthropods of medical importance. Two research contracts with the University of Leiden are concerned with the acquisition of homozygous typing cells and antisera to HLA-A,B, and C loci and b cells.

### Nigeria

Ohio State University has an active ICIDR exploratory grant with the University of Nsukka to study the biological control of mosquitoes that transmit malaria by Bacillus thuringiensis. A Nigerian Visiting Fellow at the NIAID is carrying out investigations on the binding of red blood cells infected with malaria to the endothelium of blood vessels. The NIAID also participated actively in the biomedical research component of the U.S.-Nigeria Joint Task Force on Health Cooperation.

### Pakistan

Although the University of Maryland International Center for Medical Research at the Pakistan Medical Research Center (Lahore) terminated in May 1980, the NIAID maintains an active project with the University of Maryland on the ecology of mosquitoes in Pakistan and the genetic control of Anopheles culicifacies, an important vector of malaria in that country.

### Panama

During FY 1982 the NIAID supported the GML through the Gorgas Memorial Institute (Washington, D.C.) for investigations in Panama on the transmission and reservoirs of the St. Louis virus in tropical ecosystems. The GML also collaborates with the NIAID-supported Yale Arbovirus Research Unit on the epidemiology of the yellow fever virus. Intramurally, the NIAID maintains a collaborative relationship with the GML on longitudinal studies of viral gastroenteritis in infants and young children.

### Papua New Guinea

The NIAID supports entomologists through a domestic grant to the Bernice P. Bishop Museum (Hawaii) to collect and characterize larval trombiculidae (Acarina) in Papua New Guinea. NIAID scientists are developing a proposal to carry out population-based field studies on malaria in association with the Papua New Guinea Institute of Medical Research.

### Peru

The Ministry of Health has recognized the Instituto de Medicina Tropical ("Alexander von

Humboldt Institute") of the Universidad Peruana Cayetano Heredia, as the national research center for infectious and tropical diseases. The NIAID maintains regular contact with the institute.

### Poland

In October 1981 the Chairman of the Coordinating Commission for Polish-American Scientific Collaboration visited the NIAID to discuss active projects in the Polish-U.S. Agreement on Cooperation in the Field of Health. At present there are two active projects with extramural scientists on the immunochemistry of Shigella lipopolysaccharides and on the role of macrophage surfaces in the regulation of immune response.

### Sierra Leone

The NIAID and FIC completed an interagency agreement with CDC for studies in rural Sierra Leone on Mastomys natalensis (a multimammate mouse) and Lassa fever. The project characterized the populations of M. natalensis in and around villages, determined the relationship of genetic subpopulations of mice to transmission of Lassa fever to humans, described the epidemiologic and socioeconomic factors associated with transmission in the village, and developed strategies to prevent rodent-human transmission.

### South Africa

The NIAID currently supports a research contract with the State University of New York (Syracuse), which provides for collaboration with the Bureau of Biologics (BOB) of the Food and Drug Administration, the South African Institute for Medical Research (Johannesburg), and the University of Cape Town to test the efficacy of the new BOB meningococcus, type B polysaccharide vaccine in infants and young children during the ongoing epidemic of that disease in South Africa. Safety and efficacy studies had previously been carried out in U.S. children at NIAID Vaccine Evaluation Centers at Baylor University and the University of Vermont. The NIAID continues a long-standing collaboration with the Division of Veterinary Services (Onderstepoort) on the systematics and vectors of parasitic arthropods.

### Spain

An NIAID scientist was a member of the four-person U.S. team that assisted the Spanish Government in October 1981 with the investigation, management, and control of the toxic poisoning associated with an adulterated batch of commercial olive oil.

The NIAID Associate Director for International Research visited the Ministry of Health and the Centro Nacional de Microbiologia, Viriologia, e Immunologia Sanitorias (Majadahonda) to discuss opportunities for participation in the U.S.-Spain Science and Technology Program.

#### Sri Lanka

An NIAID scientist visited Sri Lanka in October 1981 in conjunction with a workshop entitled "Diagnosis, Evaluation, and Control of Lymphatic Filariasis."

#### Sudan

Through an ICIDR Program project award, Michigan State University is collaborating with the Ministry of Health on the clinical trials of new antischistosomal drugs (e.g. oltipraz), the in vitro cultivation and drug-sensitivity testing of malarial strains from the Sudan, the ecology of Simulium damnosum, and the epidemiology of human onchocerciasis. Collaborative arrangements have been made with the WHO Malaria Training Center (Sennar), USAID, Rhone Poulenc (Paris), and West German investigators.

An NIAID scientist visited the Sudan to determine whether a collaborative study on leishmaniasis might be feasible and to attend a 1-day review in Khartoum of the ICIDR project. Collaborative investigators gave presentations regarding administration of the program and technical reports on schistosomiasis, onchocerciasis, and malaria.

A recent article in Science reported that sera collected from individuals living in malarious regions of the Sudan not only contained merozoite-blocking antibodies but also caused intracellular parasite deterioration and classical crisis forms in cultures of P. falciparum. This ICIDR award has also produced 6 additional papers in press and 12 abstracts of papers presented or about to be presented at national meetings.

#### Sweden

The NIAID continued discussions with Swedish health authorities on bilateral epidemiologic research opportunities in the Stockholm County Health Care Information System and in the NIAID/USAID Regional Project entitled "Epidemiology and Control of Vector-Borne Diseases in the Near East." At present, the NIAID and Swedish intramural scientists are collaborating in two areas: one with the Universities of Lund and Uppsala on the molecular aspects of mycoplasma-eukaryocyte interactions and the other with the University of Uppsala on the structural and functional relationships of bacterial antigens in the immune response.

#### Switzerland

NIAID intramural scientists are actively collaborating with Swiss investigators at Basle on the immunology and chemotherapy of systemic mycoses and at Neuchatel on the natural history and public health significance of a previously unrecognized rickettsia in the Ixodes ricinus tick similar to the Rocky Mountain spotted fever agent. An investigator-initiated grant to the University of Zurich supports studies on the in vitro and in vivo specificity of virus immune T cells. A new training grant provides research training at the University of Geneva on the cloning of murine histocompatibility-2 genes.

#### Tanzania

The Director of the National Institute of Medical Research (Dar el Salaam) visited the NIAID in July 1982.

#### Thailand

The University of Illinois ICIDR Program project award involves collaboration with the Universities of Cincinnati, New Mexico, and Chiang Mai and the McKean Rehabilitation Institute. It includes four interrelated areas: epidemiology and seroepidemiology of leprosy infection and disease, genetic studies of susceptibility to leprosy, immunoregulatory abnormalities and immunopathology of leprosy, and phagocytic cell functions and metabolism in leprosy.

#### Trinidad and Tobago

Rockefeller University has received an NIAID grant to continue collaborative studies with Trinidadian investigators on the streptococcal nephritogenic protein derived from the serum of patients with acute, post-streptococcal glomerulonephritis (AGN). Serum collected from healthy children patients with impetigo, and AGN will be tested by ELISA and RIA to determine the prevalence of this protein at different ages, the presence of antibody, and the protective role of the antibody against AGN.

Investigators at Northwestern University and the Streptococcal Disease Unit (San Fernando, Trinidad) reported in the New England Journal of Medicine on a 12-17-year followup on patients with AGN in which only 3 of 760 patients developed chronic renal disease.

#### U.S.S.R.

NIAID's formal involvement in the U.S.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Science and Public Health has been limited to influenza. This initiative, under



CDC coordination, provides for exchange of information, scientific meetings, visits by scientists, and a mutual exchange of virus strains and laboratory reagents. During FY 1982 the NIAID initiated collaborative activities to identify new hepatitis agents with the Institute for Polio-myelitis.

#### United Kingdom

The Medical Research Council Clinical Research Center (Harrow) collaborates with the NIAID on the electron microscopy of bacteria and on mycoplasma. The London School of Tropical Medicine and Hygiene is collaborating with the NIAID on the role of bacterial antigens in immune response. The NIAID has initiated collaboration with the Wellcome Research Laboratories (Kent) on the developmental adaptations of *T. cruzi* in vertebrate immune systems. One extramural research grant to the Institute of Animal Physiology deals with the genetics of response to histocompatibility antigens. Four English scientists hold NIAID-supported research training grants in diverse areas.

#### Venezuela

Because 9 of the 10 priority areas in the biomedical and epidemiological research component of the draft U.S.-Venezuelan Joint Health Agreement are communicable diseases, the Director, NIAID, has agreed to serve as the interim coordinator. In July 1981 visits were made to the Pan American Center for Research and Training in Tropical Diseases (CEPIALET), the Venezuelan Institute of Scientific Investigation (IVIC), the Tropical Medicine Institute (IMT), the Torrealba Institute, the National Institute of Health (INH), and "La Trinidad" Medical Teaching Center to determine the present level of scientific exchange and opportunities for new and expanded collaboration.

The Venezuelan Communicable Disease Coordinator and Director of CEPIALET has since visited the NIAID, and an NIAID scientist attended a workshop entitled "Immunotherapy and Pathogenesis of Leprosy" at CEPIALET. The Venezuelan health coordinator and Director, INH, visited the NIAID, and the Director of the Torrealba Institute initiated discussions on collaborative research in Chagas' disease.

In August 1982 NIAID scientists spent several weeks at CEPIALET to conduct immunologic studies on Venezuelan patients with disseminated cutaneous leishmaniasis and to evaluate the effect of heat therapy in inducing remissions. CEPIALET has also initiated joint studies with Tulane University on the effect of Albendazole in the treatment of patients with onchocerciasis. The NIH and CDC have initiated collaborative work with the Ministry of Health and Zulia health officials to characterize the delta agent

producing lethal hepatitis among isolated Amer-indian populations. NIAID intramural scientists continue joint investigations with researchers at the University of Caracas in epidemiological, clinical, and biochemical studies of human enteroviral infection.

A Venezuelan delegation visited the NIH, the FDA, Wistar Institute, and Wyeth Laboratories to discuss collaboration on the development and production of improved rabies vaccines.

#### Zambia

The NIAID continues long-standing scientific exchange with the Tick Diseases Unit (Lusaka) in the morphology and classification of African specimens. In May 1981 the WHO Team Leader of the Tropical Disease Research Center (Zambia) visited the NIAID.

#### Zimbabwe

Following a visit from the Secretary of the Ministry of Health in September 1980, the NIAID has begun an exchange of scientific information with the Blair Research Institute. An NIAID Staff Fellow spent 3 months on the Infectious Diseases Service of the University Hospital (Salisbury).

### Activities With International Agencies

NIAID intramural laboratories serve as WHO Collaborating Centers in rickettsial diseases, mycoplasma, and respiratory viruses other than influenza. During FY 1979, WHO designated the NIAID Microbiology and Infectious Diseases Program as one of three collaborating centers on interferon. The NIAID extramural program also provides indirect support to U.S. institutions that serve as WHO Collaborating Centers. Among the most active are WHO Collaborating Centers in arboviruses (Yale), enteroviruses (Baylor), influenza (CDC and St. Jude's Children's Research Hospital), and immunology (Scripps Clinic). At the invitation of WHO and TDR, NIAID staff and awardees participated actively in meetings or expert panels, as consultants to WHO or member countries, or as faculty in WHO-sponsored training activities. NIAID staff are particularly active in support of the WHO Immunology Program, which includes participation in the annual WHO Immunology Course in Lausanne.

### Extramural Programs

The NIAID extramural portfolio in tropical medicine is drawn from nine areas of the Microbiology and Infectious Disease Program: the six tropical diseases, ICIDR and TRU Programs, general parasitology, tropical virology, tropical



bacteriology, tropical mycology, rickettsiae, and vector pathogens.

Between 1960 and 1980 the NIAID supported an ICMR Program, established under the authority of P. L. 86-610. An ICMR was a research organization sponsored by a U.S. health institution to provide a stable base for research and training through overseas research centers. The four ICMR units in Kuala Lumpur (Malaysia), Dhaka (Bangladesh), Lahore (Pakistan), and Cali (Colombia) collectively served as a national resource to provide a pool of tropical disease investigators and to stimulate young scientists to pursue careers in international biomedical research.

The ICMR Program, however, has been superseded by four award mechanisms that provide greater flexibility and cooperation between U.S. tropical medicine specialists and their counterparts in developing countries. These mechanisms are the International Collaboration in Infectious Disease Research Program, the Tropical Disease Research Units, the International Tropical Disease Research Fellowships, and the Senior International Fellowships with an emphasis in tropical diseases.

The ICIDR Program differs from the ICMR Program in several ways. Perhaps the most important is the ICIDR emphasis on developing peer relationships between U.S. institutions and investigators and their counterparts. Its focus is on infectious diseases, and at least 70 percent of the award must be spent overseas. The ICIDR Program has two parts: the program project (Part A) provides grants for collaborative research in a series of related projects and the exploratory project (Part B) divides grants between individual scientists in a single area. In 1982, Part A awards linked Harvard and Cornell Universities with the Federal University of Bahia, Brazil; the University of Illinois with Chaing Mai University in Thailand; Michigan State with Central Laboratories of the Sudanese Ministry of Health; and the Tulane School of Public Health with institutions in Colombia and Haiti. Part B developmental grants linked Columbia University and the University of South Florida with two Brazilian institutions; the University of Washington with the National Polytechnic Institution in Mexico City; Ohio State University with the University of Nigeria, Nsukka; and the University of Hawaii with the University of Aligarh in India.

For many years NIAID intramural laboratories, particularly the Laboratory for Parasitic Diseases and the Rocky Mountain facilities, have been committed to basic research in tropical diseases. With NIAID support, the Yale Arboviral Research Unit also provides a university-based center of excellence in tropical virology. The

NIAID-funded Tropical Disease Research Unit Program is designed to expand this network to outstanding U.S. institutions through awards for multidisciplinary research in tropical medicine. In addition to generating new knowledge, the TRU Program provides the opportunity for institutional strengthening, research training for young U.S. and foreign scientists, career development, and a domestic counterbalance to the ICIDR initiative overseas. In FY 1982, the TRU award to the Peter Bent Brinham Hospital at Harvard and to Case-Western University continued.

The ITDR Fellowship Program was initiated in 1979 with NIAID funds to provide a limited number of postdoctoral fellowships for scientists from developing countries for advanced U.S.-based research training in tropical disease. Applications were encouraged from developing countries that may not be participating in the FIC-supported International Research Fellowship Program. The TDR Program has cooperated in screening and identifying candidates for ITDR fellowships. WHO also provides international travel funds for successful candidates it has nominated. In FY 1982 an Indian and a Peruvian scientist completed the first two ITDR awards for research training in leprosy and malaria, respectively. Two new awards were made with FY 1982 funds for a Chinese and an Egyptian scientist to enter schistosomiasis research training at the University of Pennsylvania.

The Senior International Fellowship, with an emphasis in tropical diseases, provides 3-12 months of research support for mid-career and senior U.S. scientists to conduct collaborative tropical disease research projects outside the United States. The initial three awards supported research in Kenya, the Netherlands, and the United Kingdom during FY 1981-82.

The Immunology, Allergic and Immunologic Diseases Program is the other major NIAID extramural awards program. Advances in immunology have increased IAIDP international activities with most industrialized countries. Relatively recently, interest has grown in involving the larger and/or more advanced developing nations such as China, India, Thailand, and Venezuela in direct cooperation in immunology or in application of new research tools to serious endemic disease problems.

IAIDP now coordinates 18 domestic asthma and allergic disease centers and four centers for interdisciplinary research on immunologic diseases. These constitute a network of U.S. investigators for research training and collaboration. IAIDP also supports five lymphocyte biology centers and in FY 1982 established the first program project at Johns Hopkins University to study immune function in transplant



recipients. During FY 1982, the IAIDP Hybridoma Cell Line Bank, established at the American Type Culture Collection, continued to acquire cell lines and began distribution to qualified investigators.

Other IAIDP-supported activities include the Allergen Research Reference Laboratory (Mayo Clinic), the International Bone Marrow Transplantation Registry (Mt. Sinai, Milwaukee), and the Histocompatibility Serum Bank. Countries participating in these programs during FY 1982 included China, France, the Federal Republic of Germany, Japan, the Netherlands, Switzerland, and the U.S.S.R.

Non-U.S. scientists may compete for NIAID grant awards and apply directly for "sole-source" contracts in any program area. Of the 23 awards made in FY 1982 to investigators in 10 countries, only 3 were relevant to tropical medicine. No principal investigator came from a developing country. The 23 foreign awards in FY 1982 represent a significant decline over the past 3 years: 27 awards were made in FY 1981 and 46 in FY 1980.

Although the major functions of the NIAID Extramural Activities Program are program analysis, project review, and grant or contract management, its Research Resources Branch also coordinates the Institute's continuing efforts to provide reagents and resources to investigators and government agencies throughout the world. During FY 1982 this activity amounted to 11 major grants or contracts for the distribution of microorganisms, parasites, or animals for research relevant to tropical medicine; in this area, 7 fewer awards were made than in FY 1981. Also, reduced costs resulted from phase-outs, transfers of functions outside the NIAID, consolidations, and the less frequent provision of reference materials from intramural laboratories.

In addition to these activities in tropical medicine, this branch continues to provide research and reference reagents not available through commercial sources for enteroviruses, adenoviruses, rhinoviruses, myxoviruses, the agents and antigens of hepatitis A and B, coronaviruses, herpesviruses, interferons, mycoplasmas, and reoviruses. During FY 1982, arrangements were made with the Plum Island Animal Disease Center to process the immune ascitic fluids of African swine fever, Rift Valley fever, African horse sickness, and bovine ephemeral fever. Complement Compound C<sub>3</sub> and penicillin products are provided in association with the American Type Culture Collection. Hypersensitivity pneumonitis antigens and antisera are being made available in cooperation with the Mayo Clinic. Additional allergenic products made available include ragweed and rye grass

antigens and venoms from honey bees, hornets, yellow jackets, and other hymenoptera.

### **Intramural Programs and Activities**

The NIAID intramural program now has 13 research laboratories or branches, three of which are located at the Rocky Mountain facilities in Hamilton, Montana. Although all of these laboratories have significant international health activities, the major portion of tropical medicine research is concentrated in the Laboratory of Parasitic Diseases. The Epidemiology Branch of the Rocky Mountain Laboratory also sets aside a substantial portion of its resources for medical zoology and vector studies.

At Bethesda, the Laboratory of Infectious Diseases increasingly emphasizes collaborative investigations into respiratory viruses, diarrheal diseases, and hepatitis.

Recent advances in immunology and laboratory techniques are now being applied to diseases prevalent in the tropics with a consequent tendency for broader involvement by basic biomedical research laboratories in international research. The Laboratory of Microbial Immunology, for example, is active in studying the immune reaction to several parasitic infections such as trypanosomes, malaria, and amebae in experimental models. The Laboratory of Clinical Investigation and the facilities at the Clinical Center are available for detailed studies on U.S. or foreign patients with known or suspected tropical diseases.

While the actual level of intramural research in tropical medicine increased by only 7 percent between 1981 and 1982, this support is enhanced considerably through NIAID intramural investigators' collaboration with colleagues outside the United States. This joint research extends to many areas beyond the scope of tropical medicine in the exchange of scientists, data, diagnostic material, or the introduction and standardization of laboratory techniques. Collaboration immediately relevant to Tropical Medicine also occurs within the NIH and with other Federal agencies, particularly the Centers for Disease Control, the Office of Naval Research, the Walter Reed Army Institute of Research, and the Bureau of Biologics. Intramural scientists are also involved in the technical work of bilateral (USAID), multilateral (WHO, PAHO), or private (Rockefeller Foundation, National Academy of Sciences) agencies concerned with tropical medicine and international research.

In FY 1982, 30 intramural projects included significant collaboration with scientific institutions in 27 foreign countries. The most frequent collaborators were from France and

Switzerland, followed by India and the United Kingdom. Australia, Canada, Egypt, the Federal Republic of Germany, Ghana, and Japan each had two cooperating units. One unit also existed in Belgium, Brazil, the Dominican Republic, the German Democratic Republic, Israel, Italy, Panama, Puerto Rico, Sweden, and the U.S.S.R.

### Visiting Program

The NIAID intramural program benefits considerably from the participation of foreign visiting scientists. In FY 1982, for example, the NIAID provided funds for 71 long-term visiting scientists and 5 experts from 26 countries. The NIAID provided laboratory space and reagents for 33 guest scientists whose salaries were paid by their home institution, government, or source other than the NIH. The largest number were from Japan (19), the United Kingdom (10), India (9), China (8), and Australia (7). Smaller numbers represented France (6), Brazil (5), Argentina (4), and Taiwan (4). There were three scientists from Germany (Federal Republic), Nigeria, and Sweden; two from Israel, Italy, Korea, Switzerland, and Venezuela; and one from Bangladesh, Can-

ada, Colombia, Denmark, Hungary, Lebanon, Mexico, the Netherlands, the Philippines, Sierra Leone, South Africa, the U.S.S.R., and Yugoslavia.

### International Conferences, Seminars, and Meetings

During FY 1982 the NIAID organized, funded, and actively participated in a variety of scientific meetings relevant to tropical medicine and international research. Almost a dozen meetings were major national and international meetings, conferences, and congresses concerning research issues such as interferon, sexually transmitted diseases, measles immunization, diarrheal diseases, and infectious and parasitic diseases. An additional 14 meetings related to bilateral research programs, 10 of which were associated with various activities of boards working under the U.S.-Japan Cooperative Health Program or programs in Latin America, the Caribbean, and the Middle East. Also, a number of conferences, seminars, and meetings were held in connection with support of research under the auspices of such organizations as WHO, PAHO, and USAID.

NIH LIBRARY



## Chapter X

# National Institute of Child Health and Human Development

### Introduction

The mission of the National Institute of Child Health and Human Development (NICHD) is to conduct and support research on the reproductive, developmental, and behavioral processes that determine the health of children, adults, families, and populations.

The Institute's programs stem from the assumption that adult health and well-being are determined in part by episodes in early life, that human development is a continuous process throughout life, and that reproductive processes and the management of population problems are of major concern, not only to the individual but also to the whole of society.

The NICHD supports research in the reproductive sciences that enables men and women to regulate their fertility with methods that are safe, effective, and acceptable to various population groups and to overcome problems of infertility. In the social and behavioral sciences, Institute-sponsored research is aimed at understanding the causes and consequences of population change. Research for mothers, children, and families is designed to advance knowledge of fetal development, pregnancy, and birth; to identify the prerequisites of optimal growth through infancy, childhood, and adolescence; and to contribute to the prevention and treatment of mental retardation.

The pursuit of new knowledge is basic to the Institute's mission. The NICHD regards international cooperation as a catalyst for the development of that new knowledge. Through a variety of mechanisms, the Institute has maintained and expanded its activities in the international exchange of scientific information. Activities are conducted under bilateral agreements and the Special Foreign Currency (P.L. 480) Program and in cooperation with international agencies and the NIH Visiting Program.

In addition, the NICHD directly supports foreign investigators through research grant and contract awards to their home institutions and indirectly through awards to U.S. institutions with foreign components or involvement in foreign research.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

##### China

In January 1979, the United States and China signed an Agreement for Cooperation in Science and Technology. The agreement, containing specific allowances for cooperative activities in a number of scientific fields, was furthered in June 1979 when health officials from both countries signed the Protocol for Cooperation in the Science and Technology of Medicine and Public Health. Areas of cooperation between the NICHD and counterparts in China include human genetics, public health and health services research, child development and nutrition, and reproductive physiology and family planning.

As a followup to the 1981 visit to China by NICHD staff participating in the U.S. Delegation on Reproductive Physiology and Family Planning Techniques, a plan for a study on pregnancy outcomes has been designed for implementation in Shanghai County. The Institute has forwarded the study--which includes perinatal mortality, low birth weight, and congenital malformations--through channels to the Chinese Coordinator.

##### India

In accordance with the Indo-U.S. Bilateral Agreement dating from 1974, and in cooperation with the U.S.-India Subcommission on Science and Technology and the India Council for Medical Research, the NICHD staff has participated in meetings to advance collaborative research in the population sciences and in nutrition. A Working Group on Reproduction and Contraceptive Research oversees the development of the cooperative program.

## Japan

The NICHD participates in the efforts of the U.S. Malnutrition Panel Program of the U.S.-Japan Cooperative Medical Sciences Program by supporting research studies intended to develop solutions to the nutritional problems of special concern to Asian people.

## Nigeria

In September 1981, Nigeria and the United States signed a formal agreement to establish cooperative health activities. The plan specifies U.S.-Nigeria research collaboration in nutrition, beginning with workshops to develop preliminary research protocols, followed by workshops in the United States that will include Nigerian investigators.

## Poland

Under the U.S.-Poland Collaborative Research Agreement, a study of the epidemiology of neural tube defects continues at the Krakow Institute of Pediatrics.

## Yugoslavia

A collaborative study of breast cancer as a possible result of oral contraceptives is in progress with the Institute of Oncology in Ljubljana, under the U.S.-Yugoslavia Joint Board for Scientific and Technological Cooperation.

## Activities With International Agencies

### World Health Organization

NICHD staff serve as consultants to the WHO Special Program of Research, Development and Research Training in Human Reproduction and as members of the WHO Committee on Resources for Research about Human Reproduction.

Collaborative and cooperative efforts with WHO on the development of safe and effective methods of fertility regulation for both men and women have been extensive. These activities range from mutual consultation to joint product development.

### European Medical Research Council

Staff of the NICHD are members of the council's Advisory Subgroup on Reproduction, which was established to identify areas of cooperation within Europe and between Europe and the United States on research in reproduction. The

subgroup also interacts with the pharmaceutical industry to obtain information about the industry's research projects with a possible bearing on human reproduction.

## Extramural Programs

Components of the NICHD extramural research program are the Center for Population Research, the Center for Research for Mothers and Children, and the Epidemiology and Biometry Research Program.

The Center for Population Research is responsible for the primary Federal research effort in the population sciences. Included are studies on human fertility and infertility, the development and evaluation of methods of fertility regulation, and the social and behavioral aspects of these problems in relation to individuals and to populations. Through research grants and contracts, the NICHD supports investigators around the world.

A research project supported by the Center for Population Research is studying the motivations and adjustments of migrants from a rural region in the Philippines who resettled either in Manila, the major urban area of the country, or in Honolulu, a key U.S. destination city. The study has provided new insights into the reasons for moving, the choice of destinations, and the effect of migration policies on internal and international migration flows.

Migration decisions, the study shows, are based on a complex set of familial and quality-of-life consideration, and are not dictated simply by economic circumstances. The study found that household and family strategies influence decisions about moving to a greater extent that individual desires do. Out-migrants often maintain substantial obligations and continuing contacts with their previous households through monetary remittances, visits, and correspondence. The study also confirmed the importance to decisionmaking of assistance from relatives and friends located in different potential destinations.

The Center for Research for Mothers and Children supports biomedical and behavioral research aimed at making possible pregnancies and births that produce sound infants, who can grow to adulthood free of disease and disability. Since its inception, the NICHD has promoted research on the role of nutrition in the prevention of disease and disability as part of the strategy for achieving that goal.

A nutritional anthropologist is currently studying the relationship between culturally induced malnutrition in young children and protection against malaria in the Sudest Island of



New Guinea. Malaria, endemic in this area of New Guinea, represents a major cause of childhood mortality. Feeding animal protein to children under age three is traditionally proscribed. The resulting malnutrition produced by this prohibition may offer protection against the malaria plasmodium, which appears to be more sensitive to undernutrition than the human host. The current working hypothesis is that traditional food taboos among these islanders represent a cultural adaptation to the local environment.

This observation in the field has implications for developing more sophisticated single nutrient deficiencies in the human host to protect against disease. For instance, iron depletion by lactoferrin in the gastrointestinal tract of human newborns may reduce or alter the resident bacterial colonies there.

The Center for Research for Mothers and Children also supports studies on the human learning process and communicative disorders. A researcher in England is measuring the impact of otitis media with effusion (middle ear infection, OME) on the educational/communications competence of English-speaking children. The study will determine if persistent OME is associated with educational and/or linguistic retardation, what types of problems may result, and if ways can be found to provide early detection of such problems.

The Epidemiology and Biometry Program is collaborating with the Department of Epidemiology at Ben Gurion University, Beer Sheva, Israel, in a study of the effects of westernization on infant feeding practices among Bedouin populations undergoing transition from a nomadic to a more settled lifestyle. Data are being collected to test the hypothesis that, as this transition takes place, less exclusive breast feeding and more bottle feeding and mixed breast and bottle feeding will be practiced. This study examines the effects of infant feeding, use of health services, and other aspects of a changing lifestyle on the rate of growth and morbidity during the first year of life.

Collaboration is continuing with the University of Trondheim in Norway to study the outcome of successive pregnancies. The routine linkage of vital record systems in Norway with death record systems, available now for over a decade, provides unusual opportunities for epidemiological investigation of birth outcome. Similar linkage has occurred more recently in Sweden, and the Epidemiology and Research Program has developed collaborative contacts with the University of Uppsala in exploring these data systems.

## **International Conferences, Seminars, and Meetings**

Collaborative endeavors with WHO in the area of fertility regulation continued in 1982 with a "Consultation on the Chemical Synthesis of Fertility Regulating Agents" held at the NIH and cosponsored by WHO and the NICHD.

NICHD staff attended the European Medical Research Council symposium in Paris entitled "Epidemiological Aspects of Human Reproduction," which included a session on fertility and sterility.

## **Intramural Programs and Activities**

NICHD intramural scientists engage in international collaboration in research projects relevant to their own research interests at the NIH. Often these collaborations are formal, structured, and endure for many years. For example, one NICHD laboratory chief serves as genetic coordinator with China under the U.S.-China Health Protocol.

Research opportunities within the Intramural Program of the NICHD include clinical studies in the areas of human genetics, endocrinology, and reproductive physiology, as well as developmental psychology.

## **NIH Visiting Program and Health Scientist**

### **Exchange Programs**

The NIH Visiting Program provides opportunities for recent postdoctoral fellows and senior scientists from abroad to conduct collaborative research in the United States. More than 50 internationals from a dozen countries were involved in the NICHD Intramural Research Program during 1982. The usual length of the visit is 2 to 3 years. In addition to participants in the formal Visiting Program, there are a large number of foreign visitors who come as guest workers, whose financial support comes from sources other than the NICHD.

The activities of all these scientists are pursued in 11 basic science laboratories or clinical research branches of the NICHD, including the Developmental Pharmacology Branch, the Endocrinology Branch, the Laboratory of Developmental Neurobiology, the Laboratory of Neurochemistry and Neuroimmunology, the Laboratory of Theoretical Biology, the Human Genetics Branch, and the Laboratory of Developmental and Molecular Immunity.

# Chapter XI

## National Institute of Dental Research

### Introduction

In the search for a better understanding of oral health and disease--problems that recognize no barriers of geography--the promotion of dental research internationally cannot be separated from the promotion of dental research domestically. The National Institute of Dental Research (NIDR) encourages the programming of grants, contracts, and intramural research wherever the best data sources and expertise lie. The Institute emphasizes staff participation in and support of international meetings and the publication of proceedings, the funding of foreign grants and contracts, and the provision of research opportunities for visiting scientists.

In its mission to support and facilitate research on the etiology, diagnosis, prevention, and treatment of oral diseases and malfunctions, the Institute's six major program areas serve as the central force for programming: dental caries; periodontal diseases; craniofacial anomalies; soft tissue, stomatology, and nutrition; restorative materials; and pain-control/behavioral studies. The Intramural Research Program, organized according to basic biomedical disciplinary lines, and the National Caries Program invite visiting scientists to augment basic scientific investigations, primarily, and, to a limited extent, clinical research projects.

During FY 1982, the Institute funded nine foreign grants in the research areas of dental caries, tooth mineralization, pain control, craniofacial anomalies, and composition of connective tissue. In Bethesda, the Institute's intramural program supported or sponsored 33 Visiting Fellows, 7 Visiting Associates, and 7 Visiting Scientists. They came from 17 countries, 8 in Europe, 6 in Asia, 2 in Latin America, and 1 in the Near East.

The Institute encourages a wide exchange of scientific information. NIDR Abstracts informs dental investigators of current developments in special areas of interest. This publication is distributed to about 150 foreign colleagues. Dental scientists around the world have been asked to register their research projects with the Dental Research Data Officer of the NIDR for inclusion in an annual publication, Dental Research in the United States and Other Countries.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

Under the auspices of the U.S.-Nigeria Cooperative Health Agreement, the NIDR assisted the Nigerian Ministries of Health and Science and Technology, as well the WHO, the Federation Dentaire Internationale, and the International Association for Dental Research, in planning and conducting the Conference on Dental Research Needs and Opportunities in the WHO-Region of Africa. The conference was held in February 1982 in Lagos, Nigeria, and brought together more than 20 countries whose representatives agreed that a WHO International Collaborative Center for Dental Research and Oral Health would be an appropriate means to stimulate and nurture research in this region of the world. The Nigerian Government expressed a wish to host such a center. The protocol for the center is currently being circulated in the region to solicit financial support.

#### Activities With International Agencies

The Special Assistant to the Director, NIDR, served as a consultant to the USPHS/WHO International Collaborative Study of Dental Manpower Systems in Relation to Oral Health Status. In that capacity she was a technical advisor to the WHO Regional Office for Europe to explore the implications of the collaborative study for the delivery of dental services in northern and western Europe.

#### Extramural Programs

International collaboration during the year continued or was initiated between NIDR scientists and researchers at the following institutions by means of grant support:

- University of New South Wales and the Institute of Dental Research, Sydney, Australia (surface structure of oral bacteria);



- University of Queensland, Brisbane, Australia (surface composition of apatites);
- McGill University, Montreal, Canada (pro-collagens in dental tissues);
- University of Toronto, Canada (brain stem mechanisms and dental pain associated with trigeminal nucleus caudalis);
- College de France, Paris (migration and differentiation of neural crest cells);
- Gothenburg University, Sweden (plaque control and healing after periodontal surgery); and
- Hebrew University of Jerusalem, Israel (mineralization of tooth enamel).

### **International Conferences, Seminars, and Meetings**

In 1982, 29 NIDR scientists attended and contributed to 57 meetings in 21 foreign countries and 5 continents. Of these meetings, 19 were seminars and discussions of collaborative research. The other occasions were workshops, symposia, and conferences such as the Tenth Sao Paulo Congress of Odontology and Latin American Seminar of Odontology-Sao Paulo, Brazil; the Twelfth European Leucocyte Culture Conference-Vienna, Austria; the First Erik Fernstrom Symposium (neurology)-Lund, Sweden; a Ciba Foundation Symposium (protein chemistry)-London, England; the Third Merieux Conference on the Pathology of Viral Diseases-Lyon, France; the Conference on Genetics of Industrial Microorganisms-Kyoto, Japan; and the International Sociological Association Symposium on International Collaborative Research in Health-Mexico City, Mexico. The NIDR also provided support to enable foreign scientists to give papers at four conferences in the United States.

NIDR staff of the National Caries Program planned and hosted the first U.S. meeting of the European Organization for Caries Research, in Annapolis, Maryland, in June 1982 in honor of the tenth anniversary of the establishment of the National Caries Program. The Special Assistant to the Director chaired the International Relations Committee of the International Association for Dental Research and participated actively in promoting dental research capacity in developing countries. She also assisted the Division of Health Policy Research and Education at Harvard University through a cooperative assignment to develop initiatives on international aspects of health and human behavior in developing countries, and on issues of health science policies related to the allocation of resources for

research in industrialized societies. She prepared agenda items on issues of international health policy relevant for pursuit by the NIH and/or academic institutions.

### **Intramural Programs and Activities**

The microbial systematics section of the Institute continues to collaborate with the American Type Culture Collection, the Centers for Disease Control, the FDA, the VA, and numerous researchers in foreign counterpart organizations in regard to the worldwide data bank for information on the diverse strains of human oral microbiota.

The system devised for bacteria has now been expanded to include other organisms such as yeasts, molds, algae, protozoa, and hybridomas so that confusing relations among these life forms can be systematized and certain controversial epidemiological data can be clarified. Also, to help identify unknown bacteria isolated from the mouth, computer-aided patterns or matrices have been constructed and are available to researchers throughout the world.

An NIDR scientist is collaborating with an Israeli investigator, at the Weizmann Institute, who is crystalizing osteonectin--an important protein in bone matrix--in order that the protein's structure may be analyzed by X-ray diffraction. Understanding the three-dimensional structure of osteonectin will allow scientists to determine how the protein accomplishes its biological activities.

Scientists in the NIDR Laboratory of Biochemistry, collaborating with investigators at the University of Monash, Melbourne, Australia, are using the long-lasting techniques of organ culture devised by the Australians. They are studying how cartilage cells synthesize and break down, over periods of several weeks, the large proteoglycan molecules that act as shock absorbers to cushion loads on human joints.

### **NIH Visiting Program and Health Scientist**

#### **Exchange Programs**

A Visiting Fellow from Korea is collaborating with staff of the Laboratory of Microbiology and Immunology, NIDR, in obtaining circular DNA from bacteria. Genes in this DNA control the ability of bacteria to digest sugars. The genes have been cloned into other bacteria so that the molecular basis of this genetic process can be studied and so that eventually tooth decay can be controlled more effectively.

In the same laboratory, a scientist from the New Zealand Dairy Research Institute, Palmer-

ston North, has shown that a sugar variant (2-deoxyglucose) interferes with the ability of various bacteria to absorb sugars and makes it hard for them to grow. This research is potentially useful for developing sugar analogues that might be added to the diet to reduce tooth decay.

From herpesvirus type 1, the cause of fever

blisters, an English expert has isolated a gene that codes for a specific protein and has used recombinant DNA techniques to introduce this gene into a common bacterium so that the bacterium will produce the protein in quantity. These preliminary steps may result in the production of a safe vaccine against this disease.



## Chapter XII

# National Institute of Environmental Health Sciences

### Introduction

During recent decades, some of the more urgent health problems confronting the general population have arisen from human exposure to chemical and other physical factors in the environment. Health risks emanating from man's environment are not a new phenomenon. However, with the post-World War II growth in industry and commerce and the acceleration of industrialization in developing countries, recognition and concern for the potentially adverse effects of environmental agents on human health and the ecosystem have become worldwide. Public and private organizations throughout the world have tried to anticipate and avoid these problems through support of environmental health research. The National Institute of Environmental Health Sciences (NIEHS) serves as the principal U.S. Federal agency for biomedical research on the effects of chemical, physical, and biological environmental agents on human health. The research aims of the NIEHS focus on identifying and investigating environmental factors that may have deleterious effects on human health (e.g., mutations, cancer, lung disease, birth defects), on quantifying these effects, on understanding the mechanisms of the action of toxic agents on biological systems, and on developing methods for testing and predicting the toxicity of chemicals. Through these efforts, NIEHS research provides the basic information necessary for establishing disease prevention programs. These goals transcend national boundaries, and the NIEHS plays a leading role in the organization and development of international efforts to meet environmental health problems.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

##### China

Cooperation between the United States and China in environmental health was initiated during 1980 under the U.S.-P.R.C. Agreement for Cooperation in the Science and Technology

of Medicine and Public Health. The NIEHS participates in public health and health services research, which includes both environmental and occupational health concerns. Exploratory discussions with scientists from both countries have been held during exchange visits with initial discussions centering around cooperation in the following areas: biochemical and epidemiological research related to asbestosis and silicosis; biochemical and epidemiological research related to heavy metals; development and validation of short-term test methods to detect and assess carcinogens, mutagens, and teratogens in the environment; and the application of standard toxicological test methods and the extrapolation of laboratory animal data to man. During FY 1982, an intramural scientist presented a series of lectures on biochemical toxicology at the Chinese Academy of Medical Sciences in Beijing and visited Shanghai to discuss plans for future cooperation with scientists from the First Medical College of Shanghai, Fudan University, and the Shanghai Cancer Institute.

##### Egypt

Cooperation between American and Egyptian environmental health scientists is being carried out under the auspices of the U.S.-Egypt Joint Working Group on Health Cooperation. The NIEHS has been assigned responsibility for the U.S. Subcommittee on Environmental and Occupational Health of the JWGHHC. Efforts to date have consisted of a workshop held in Egypt in early 1980 to identify the biomedical impacts of technology transfer. During 1982, a series of training workshops involving 24 U.S. scientists and over 100 Egyptian scientists was held in Egypt focusing on the following areas: pesticides, trace metals, radiation, environmental management, and mutagenesis. An information unit for environmental impact assessment is also being established. This project is directed to the needs expressed by the Egyptians for information on environmental and occupational health. These activities are funded largely through the NIH Special Foreign Currency (P.L.-480) Program.

##### Italy

Cooperation between American and Italian environmental health scientists is being carried

out under the joint U.S.-Italy Memorandum of Understanding signed by the Secretary, DHEW, and the Italian Minister of Health in 1977. Since that time, there have been several exchange visits between scientists of both sides and discussions aimed at defining areas of cooperation. Under discussion are possible collaborative activities concerned with mutagenicity testing, testing of complex mixtures, long-term bioassay testing, and quantitative risk assessment.

In addition to these activities, NIEHS staff have been involved in meetings and consultations concerned with the explosion of a chemical reactor in Seveso, Italy, which resulted in exposure of a large population to dioxins.

## Japan

Cooperation between American and Japanese scientists on environmental health problems takes place under two formal agreements: the U.S.-Japan Cooperative Medical Sciences Program and the Agreement on U.S.-Japan Cooperation in Research and Development in Science and Technology. Under the U.S.-Japan Cooperative Medical Sciences Program, American environmental health scientists participate in the Panel on Environmental Mutagenesis and Carcinogenesis chaired by the Associate Director for Genetics, NIEHS. Joint areas of research focus on the detection of mutagenic and carcinogenic chemicals using both *in vitro* and *in vivo* test systems and on monitoring human populations for evidence of exposure to mutagenic and carcinogenic chemicals; joint studies on carcinogens and mutagens in the diet and dietary tract have been particularly productive. To further mutual understanding of these issues, a U.S.-Japan Workshop on Genetic Toxicology and Food Mutagens was held in the United States during FY 1982.

Under the U.S.-Japan Agreement on Cooperation in Research and Development in Science and Technology, the NIEHS participates in the toxicology program area in the counterpart working group on health. Exploratory discussions on cooperation in this program were initiated in 1980 and 1981 by an exchange of scientists so that they could become familiar with the organizations and research programs in this area. In the toxicology program area, discussions centered on cooperation in the following subjects: development and validation of short-term test methods to detect carcinogens and mutagens; development of methods to test volatile chemicals; development of methods to study mixtures of chemicals; studies on the chemical initiation and promotion of cancer; and the development of approaches to quantitative risk assessment. During FY 1982, the Special Assistant to the Director for International Affairs and the Assistant to the Deputy Director, Toxicology Research and Testing Program, visited Japan to

explore further areas of cooperation and formalize the exchange of quantitative data from Japanese and U.S. mutagenicity testing programs. In accordance with the Memorandum of Understanding with the U.S. Department of Labor, NIEHS scientists also held extensive discussions with the Japanese Ministry of Labor staff regarding scientific procedures relating to bioassay protocols and regarding arrangements for an exchange of information on chemicals tested and test results.

## U.S.S.R.

Collaboration between Soviet and American environmental health scientists is carried out under the auspices of two cooperative agreements between the United States and the U.S.S.R.

Under the U.S.-U.S.S.R. Medical Science and Public Health Cooperative Agreement, the NIEHS is the lead U.S. agency for environmental health research between the United States and the U.S.S.R. is in its tenth year. An exchange of information and workshops have been held on the following topics: developmental toxicology; biological effects of metals; behavioral toxicology; and biological effects of physical factors in the environment. The proceedings of these workshops were published in both countries, and over 50 scientific papers have been published by American and Soviet scientists on the results of environmental health research conducted under this agreement. In addition, a Russian-English Glossary of Environmental Health Terminology was published in both countries to assist communications between scientists.

A workshop was held in the United States in May 1982, entitled "Nervous System Effects of Electromagnetic Waves (0-300 GHz)." Ten U.S. scientists and eight Soviet scientists participated in the workshop held at the NIEHS. The purpose of the workshop was to discuss existing methods of evaluating the impact of electromagnetic waves in the environment on the central nervous system and behavior to select those methods that appear to be most sensitive. As a result of the workshop, a duplicate project was developed to test and standardize the methodological approaches to be used for evaluating effects on the central nervous system. A scientist from the NIEHS and one from the Bureau of Radiological Health, FDA, visited the Soviet Union in September 1982 to discuss specific details and reach an agreement on the exact procedures for exposing the animals and for measuring the above parameters.

The NIEHS also participates in the U.S.-U.S.S.R. Agreement on Cooperation in the Field of Environmental Protection, which is administered for the United States by the Environmental Protection Agency. The Director, NIEHS,



serves as the DHHS representative to the Environmental Protection Agreement and cochairman of the working group concerned with the biological and genetic effects of pollution.

### Activities With International Agencies

NIEHS staff have been active participants in WHO programs for a number of years. In 1975, WHO designated the NIEHS as a Collaborating Center for Environmental Health Effects. During FY 1982, the Institute, under the leadership of the Associate Director for Health Hazard Assessment, continued to provide advice and scientific expertise to WHO headquarters and WHO regional offices.

In 1979, WHO established the International Program on Chemical Safety (IPCS), a cooperative undertaking involving WHO, the United Nations Environmental Program, the International Labor Organization, and their respective member states. Since the signing of a cooperative agreement between the NIEHS and WHO in 1980, the NIEHS has assumed the function of lead institution within the IPCS for such activities as international evaluations of biological effects of chemicals and health hazard assessments, and review and/or validation of methods for testing of mutagenicity, carcinogenicity, neurobehavioral toxicity, and toxicity to reproductive function. Assisting NIEHS participation in the IPCS is a WHO Interregional Research Unit, established at the NIEHS in 1981.

The objectives of the IPCS are (1) to encourage international cooperation in the evaluations of the effects of chemicals on human health and on the quality of the environment; (2) to coordinate chemical testing and toxicological research to eliminate unnecessary duplication of effort; (3) to develop international protocols for laboratory testing, epidemiological studies, and risk assessment; (4) to develop international guidelines and exposure limits for chemicals in air, water, and food; and limits for hazardous chemicals in workplaces; (5) to develop response mechanisms for coping with chemical emergencies that may be international in scope; and (6) to promote training and development of manpower in areas and specialties necessary for the achievement of program goals.

The Director, NIEHS, and the Special Assistant to the Director for International Affairs, NIEHS, attended the third Program Advisory Committee of the IPCS, held in June 1982 in the U.S.S.R. The PAC is responsible for evaluating the workplans and progress of the IPCS and for providing guidance on the administrative and scientific aspects of the IPCS objectives.

The Associate Director for Genetics chaired two working groups held in Geneva during 1982 to further develop the "IPCS Collaborative Study on Short-Term Tests for Genotoxicity and Car-

cinogenicity." The purposes of the program are, on an international scale, to: (1) evaluate in vitro short-term tests for mutagenesis and carcinogenesis, (2) evaluate short-term in vivo assays for mutagenicity, and (3) develop standardized protocols for the performance of short-term tests for mutagenicity. The choice of chemicals and of participating investigators in these studies has been finalized, and provisions for distributing these compounds have been made. A mutagenesis expert from the NIEHS Cellular and Genetic Toxicology Branch also participated in these meetings.

In FY 1982, the chief of the Laboratory of Reproductive and Developmental Toxicology (LRDT) and the Head, Experimental Teratogenesis Section, LRDT, participated in an IPCS/WHO-sponsored workshop, "Methods for the Integrated Evaluation of Risks for Progeny Associated with Prenatal Exposure to Chemicals," held in Prague, Czechoslovakia. This workshop was part of an ongoing effort to help organize and participate in an international effort to identify improved laboratory and clinical approaches for detecting birth defects.

Also within the framework of IPCS, the NIEHS Office of Health Hazard Assessment (OHHA), in collaboration with the WHO Interregional Research Unit, prepared draft evaluation documents on 2,6-toluene diamine and phthalic acid esters. These drafts have been transmitted for review and revision to a number of national focal points for the IPCS. The OHHA is also responsible for the scientific editing and updating of the second volume of a WHO monograph "Principles and Methods for Evaluating the Toxicity of Chemicals."

NIEHS staff also took part in a workshop entitled "Methods for Estimating Exposure, Quantifying Risk to Human Health, and Predicting Chemical Injury to Ecosystems," organized by the Scientific Group on Methodologies for the Safety Evaluation of Chemicals in July 1982 in Rome, Italy. This group is one of the IPCS projects operated jointly with the Scientific Committee on Problems of the Environment of the International Council of Scientific Unions and the United Nations Environment Program. The objective of the group is to examine methods for the predictive evaluation of the adverse effects of chemicals on human subjects and other forms of life. This was the third such workshop.

In other WHO activities, the Chief of the Laboratory of Reproductive and Developmental Toxicology, NIEHS, continued as temporary adviser to the Toxicology Review Panel of the WHO Special Program of Research, Development, and Research Training in Human Reproduction. The review panel meets twice a year to consider the potential toxicity associated with current and future approaches to contraception. The Chief of the Laboratory of Reproductive and

Developmental Toxicology has also been invited by the Office of Occupational Health, WHO, to join an international group studying occupational hazards to reproductive functions.

### Extramural Programs

Through its extramural program, the NIEHS provided grant support to (1) the State University of Leiden, Leiden, the Netherlands, to study the induction of genetic damage by chemical mutagens; (2) the University of Western Ontario, London, Canada, to study the nature of lead-binding and mercury-binding nuclear proteins; and (3) the University of Turku, Turku, Finland, to study gastrointestinal and pulmonary metabolic functions. In addition, the Extramural Program provided funds to the WHO International Program on Chemical Safety in support of that cooperative effort.

### International Conferences, Seminars, and Meetings

To provide an opportunity for scientists from different countries to exchange research results and stimulate scientific collaboration, the NIEHS continues to support a number of conferences and seminars involving international participation. Examples of the types of seminars and conferences supported in part by the NIEHS this past year include:

- Joint American-Swedish Workshop on Individual Susceptibility to Genotoxic Agents in the Human Population
- Workshop on the Utilization of Mammalian-Specific Locus Studies in Hazard Evaluation and Estimation of Genetic Risk
- Symposium on Psoralens
- Seminar on the Role of DNA Lesions and Promotion in Organ-Specific Tumors
- Seminar on recent Electrophysiological Methods for Evaluation of Neurotoxicity

### Intramural Programs and Activities

NIEHS scientists from various intramural laboratories continue to collaborate with scientists from a number of different nations. Examples of such collaborative efforts, which are of mutual benefit and produce information important to the Institute's research goals, are listed below:

### Comparative Medicine Branch

The Chief of the Comparative Medicine Branch continues as a charter member of the International Committee on the Wasting Marmoset Syndrome. This condition bears resemblance to protein-calorie deficiency in man, and the current focus of attention is on nutrition causation. Experimental work in the United States and the Federal Republic of Germany has concentrated on diet energy content. Data from 36 participating institutions in six countries were discussed at a recent meeting held in the United States.

### Laboratory of Biochemical Genetics

The head of the Mammalian Mutagenesis Section collaborated with scientists from the Federal Republic of Germany to exchange information on chemicals that induce mutations in spermatogonia of mice, biochemical screening for mutants from offspring of treated mice, and screening for cataract mutations in mice. These efforts are extremely important to NIEHS international efforts in genetic risk assessment and monitoring of human populations.

### Laboratory of Environmental Biophysics

The laboratory continues to collaborate with scientists from the University of Buenos Aires, Argentina, on the free-radical metabolism of gentian violet by *Trypanosoma cruzi*. As the agent of Chagas' disease, this microbe infects millions of people in Argentina and Brazil alone. Because *Trypanosoma cruzi* is carried by a species of the assassin bug found in Texas and elsewhere in the American South, Chagas' disease may become established in this country.

The chief of this laboratory participated in an International Congress on Water and Ions in Biological Systems, held in Bucharest, Romania, September 1982. The interdisciplinary nature of this congress provided a valuable forum for the exchange of information with a number of different countries.

### Laboratory of Environmental Chemistry

Scientists in the Laboratory of Environmental Chemistry are collaborating with scientists from the Laboratory of Molecular Biophysics, Oxford University, England, concerning the X-ray crystallographic properties of cocrystalline states of dioxin (and related compounds) and selected proteins. NIEHS scientists are also continuing their collaboration with the Department of Pharmacology, University of Urbino, Italy, on the development of a radio-immunoassay capability for detecting dioxins applicable to the Seveso, Italy, dioxin contamination problem; and



with the Canada Center for Inland Waters on the application of this assay to sediments and fish. The reliability of this assay as a screening procedure is being evaluated and has led to the proposal that this become an American Society for Testing and Materials standard method.

#### **Laboratory of Pharmacology**

The Laboratory of Pharmacology continues its collaborative research with scientists from the University of Dundee, Scotland, in which hormonal effects on perinatal drug metabolism are being studied. With scientists from East Germany and Finland, U.S. scientists are also continuing collaborative efforts on drug metabolism by isolated skin cells. The laboratory is also collaborating with colleagues from China on a project exploring the effects of selenium deficiency on the mitochondrial toxicity of lead.

#### **Laboratory of Pulmonary Function and Toxicology**

Collaborative research efforts are being conducted with colleagues from China on the mutagenic and carcinogenic properties of nickel salts and with colleagues from Japan on the role of chromosome nondisjunction in the carcinogenic activity of diethylstilbestrol and other carcinogens.

#### **Laboratory of Reproductive and Developmental Toxicology**

Collaborative research efforts continued between the Laboratory of Reproductive and Developmental Toxicology and the University of Wurzburg, the Federal Republic of Germany, on the target organ metabolism and bioactivation of the carcinogen, diethylstilbestrol. Collaborative efforts with the University of Uppsala, Sweden, on experimental studies related to the distribution and teratology of 2,3,7,8-tetrachlorodibenzodioxin also continued.

#### **Office of the Director**

The Associate Director of the Office of Health Hazard Assessment has remained active as a member of the International Joint Commission's Committee on the Assessment of Health Effects of the Great Lakes Water Quality and is involved in the evaluation of water pollutant chemicals and their potential health effects on the populations in surrounding counties. This office also participated in an international study on biological tests in the evaluation of mutagenicity and carcinogenicity of air pollutants. The objective of this study was to examine the relevance of short-term and long-term biological tests for mutagenicity to the assessment of

human carcinogenic risk that may arise from exposure to air pollution from motor vehicle exhausts and coal combustion products.

The Associate Director for Genetics attended several meetings of the Executive Board and Commission of the International Commission for Protection Against Environmental Mutagens and Carcinogens. These meetings were devoted to planning ways the commission could develop mechanisms to foster scientific interchange and programs in test-method development, validation, and use in mass-screening programs.

By interagency agreement, the NIEHS continues to support the Environmental Mutagen Information Center at the Oak Ridge National Laboratory. The center works closely with investigators around the world in both obtaining and supplying information on environmental mutagenesis. The center has over 30,000 bibliographic entries in its data banks and remains a unique worldwide resource for information on environmental chemical mutagenesis.

The NIEHS has also established the Environmental Teratology Information Center in collaboration with the Department of Energy and Oak Ridge National Laboratory. Information on teratogenesis is collected, indexed, and made available to the biomedical community directly from the center or from the National Library of Medicine's TOXLINE. The center is a unique worldwide resource for information on teratology.

#### **NIH Visiting Program and Health Scientist**

##### **Exchange Programs**

During FY 1982, collaborative research activities were carried out in the Institute's intramural laboratories by 68 Visiting Fellows and Scientists. They came from Argentina, Australia, Belgium, Canada, China, the German Democratic Republic, the Federal Republic of Germany, Finland, France, Hungary, India, Israel, Japan, Korea, Mexico, the Netherlands, New Zealand, Poland, Sweden, Switzerland, the United Kingdom, Yugoslavia, and Taiwan. Examples of collaborative research projects include studies on the metabolism of the carcinogen 2-acetylaminofluorene in rabbit pulmonary and hepatic microsomes; drug metabolism by isolated lung cells; mechanisms of hepatic action of nonsteroidal estrogens; the intracellular binding of lead; the effects of antioxidants on DNA alkylation; the mutagenic and carcinogenic properties of nickel salts; mutagenicity test methods; biometry and quantitative risk assessment; neurobehavioral, pulmonary, and reproductive toxicity; and the effects of physical factors on the nervous system.

These research projects were mutually beneficial and produced scientific information valuable to the Institute's research goals. Also during

FY 1982, many administrators and scientists from all parts of the world visited the NIEHS to be briefed on its programs and activities.



# Chapter XIII

## National Eye Institute

### Introduction

About 40 million of the world's people are blind. The great majority of them are in the developing nations of Asia, Africa, and Latin America, but blindness is unnecessarily prevalent in the industrialized regions of the world as well. It has been estimated that at least half of all blindness can be prevented by well-planned sight conservation programs that use resources and medical knowledge already available. Mobilization of such resources requires a worldwide effort to increase public and governmental awareness of the problems of blindness, to promote the development of effective programs in countries that now lack them, and to increase the effective of programs already in existence. If a cost-effective method were found to slow down the formation of cataracts so that surgery could be delayed in the United States by 10 years alone, for instance, over \$500 million per year could be saved. In much of the developing world such a new preventive measure could lead to the elimination of the backlog of millions who are blind because cataract surgery is not logistically or economically possible.

The specific objectives of the National Eye Institute (NEI) international program are these:

- Evaluating available health technologies, promoting the most cost-effective intervention and prevention programs, and making these available to affected populations;
- Conducting collaborative applied research studies aimed at developing preventive methods for dealing with very specific eye disease; and
- Promoting the controlled clinical evaluation of research findings that appear to be effective.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

##### India

Nutritional deficiency is the leading cause of blindness in children worldwide. In India alone it is said to account for 180,000 cases. Annually 20,000 children are estimated to become blind from nutritional deficiencies, primarily vitamin A, with half of these children surviving and the other half dying within 1 year. A collaborative Clinical Research Center for the Prevention of Nutritional Blindness has been established with the National Institute of Nutrition in Hyderabad, India, to attack this problem. The Center will use U.S. and Indian research bases in an applied clinical research program. This program will identify those children who present the highest risk of becoming blind from hypovitaminosis A and other concurrent factors, determine practical ways to prevent this blinding condition, and develop more cost-effective programs that target vitamin A prophylaxis to the highest risk populations. The following collaborative projects will be carried out at the center:

- Study of the relationship of vitamin A status in the development of related keratomalacia and blindness in children;
- Analysis of the role of anterior segment collagenase activity in the development of keratomalacia;
- Comparison of the absorption of vitamin A in diarrhea treated with and without oral rehydration solution;

- Examination of the relation of vitamin A status to immunocompetence and infectious morbidity;
- Evaluation of methods for identifying subclinical vitamin A deficiency in children; and
- Determination of risk factors in the development of xerophthalmia in children.

Final approval of the research agreement formalizing this collaborative arrangement has been received from both the Government of India and the United States, and Center activities are underway. The NEI has purchased major laboratory equipment for the Center under a grant from the U.S. Agency for International Development. Two Indian scientists have completed a visit to the United States for training in special laboratory techniques supportive of the collaborative projects. Late in the year an NEI collaborator visited Hyderabad to participate in the initial activities of the first project. Follow-up visits by several other NEI collaborators are anticipated shortly.

NEI scientists and consultants continued their collaboration with the Indian Government on the Indian prevention of blindness programs. The NEI continues to provide consultants in operations research, biostatistics, and clinical ophthalmology.

NEI intramural scientists, Indian scientists and clinicians from the Aravind Eye Hospital in Madurai, and engineers from the National Aeronautics and Space Administration have been working for several years to fashion a new instrument for removing cataracts more effectively. The scientists and engineers have now developed and evaluated a technique for removal of hard cataracts through a small incision with an air turbine device. The instrument has successfully undergone preliminary tests in animals as well as *in vitro* with hard cataracts from Indian patients. In 1982 clinical tests were made on 30 patients with retinal problems and a poor prognosis for vision. After the instrument functioned without incident during these tests, it was turned over to clinicians at the Aravind Eye Hospital for further clinical development.

#### Japan

The U.S.-Japan Memorandum of Understanding on Vision Research, signed in April 1976, provides for an exchange of scientists program sponsored by the NEI and the Japan Society for the Promotion of Science. Two scientists per year from each country may be selected for the exchange--one short-term (2 weeks to 3 months) and one long-term (3 months to 1 year). Two Japanese scientists traveled to the United States under the auspices of this

U.S.-Japan Memorandum of Understanding during FY 1982.

An assistant professor of anatomy from the University of Keio, Tokyo, Japan, is spending 1 year, beginning in September 1982, working with a professor at the Yale University School of Medicine. They are collaborating on analyses of synaptogenesis of the retina in fetal monkey eyes.

Another professor spent 2 months in the United States, beginning in September 1982, visiting the NEI's Louisiana State University, and the University of California at Berkeley to work on techniques for the correction of certain corneal abnormalities. As a result of this collaboration, the scientists developed a surgical procedure composed of a photokeratometry system, epikeratophakia, and thermokeratoplasty to correct refractive error.

#### U.S.S.R.

Under the Vision Research section of the U.S.-U.S.S.R. Program for Health Cooperation, both sides continued work in the following problem areas:

- Use of Q-switched laser in the treatment of glaucoma;
- Assessment of critical flicker fusion to determine optic nerve function;
- Assessment of gratings to determine optic nerve function; and
- Clinical studies of ENKAD treatment of retinitis pigmentosa.

#### Activities With International Agencies

In FY 1982, the NEI continued its activities as a WHO Collaborating Center for the Prevention of Blindness, and the Director, NEI, continued to serve as a member of WHO's Special Advisory Panel on the Program for the Prevention of Blindness. This group has been established to advise WHO in its efforts to eliminate blindness from the world's population. At the annual meeting in Geneva, Switzerland, the advisory group discussed several major topics:

- Program activities, both regional and global;
- Activities of the WHO Collaborating Centers for the Prevention of Blindness;
- Low-cost eyeglasses project;
- Strategic approaches to prevent blindness;



- Information systems;
- Collaboration with nongovernmental organizations: current status and future approaches; and
- Membership of the WHO Program Advisory Group on the Prevention of Blindness.

Over the past year, the Program for the Prevention of Blindness, which is supported primarily by the NEI, has expanded its collection of data on blindness and its causes. During FY 1982, for example, several additional surveys of blindness were developed for Asia and Latin America.

### Extramural Programs

In FY 1983, the NEI made 22 awards to foreign institutions in eight countries. The research and training projects supported were representative of outstanding research projects in all of the Institute's major research programs: retinal and choroidal diseases; corneal diseases; cataract; glaucoma; and strabismus, amblyopia, and visual processing. Both basic and clinical research projects were included. Some examples follow:

- To compare various forms of cataract, scientists at the Oxford (England) Eye Hospital have been conducting a clinical trial involving more than 300 patients. The results of this study, which will be available in about 3 years, are expected to define optimal surgical procedures for cataract extraction and patient optical rehabilitation. The potential applicability of these findings is significant because cataract is a leading cause of blindness and cataract intervention programs are conducted worldwide, particularly in undeveloped countries.
- Glaucoma is another leading cause of blindness around the world. The reduction of blindness resulting from the disease, which depends upon development and effective distribution of antiglaucoma drugs, requires a better understanding of the neuropharmacology of the eye. Two world-renowned scientists at the University of Uppsala, Sweden, have contributed significantly to developing basic knowledge of the physiology and pharmacology of the eye. Their findings have led to development and testing of new drugs for this devastating eye disease.
- Tens of thousands of infants are born each year with congenital cataracts. Although the number and scope of programs for

cataract extraction have been increasing worldwide, only a small number of children with congenital cataracts are treated early in life. The result is an irreversible visual deficit for many children. To define the critical period in visual development beyond which irreversible vision loss occurs, investigators at the Hospital for Sick Children in Toronto, Canada, are evaluating children who have had congenital cataracts extracted. Results from these studies will help define the optimal time for intervention. Such information will help eye surgeons and health care delivery organizations set priorities among the various social and economic factors that affect blindness intervention programs in developing countries.

### International Conferences, Seminars, and Meetings

The Director of the NEI participated in a course entitled "Community Eye Health" at the Department of Preventive Ophthalmology, Institute of Ophthalmology, University of London. At this course he presented a seminar on clinical trials.

A joint WHO/NEI informal workshop on cataract epidemiology was held at the NEI in June 1982. Most of the participants at this workshop were representatives of WHO Collaborating Centers for the Prevention of Blindness. Because of the rapidly growing impact of cataract, due to the generally increased life expectancy and aging of populations in developing countries, the possible prevention of this disease is gaining more attention. In this context, epidemiological studies are of particular importance. To assess possible risk factors in the formation of cataract, the participants discussed the following topics:

- Available epidemiological data;
- Identification of risk factors;
- Classification of cataract;
- Biochemical aspects of cataract epidemiology; and
- Designs for cataract research.

The NEI helped support the WHO Annual Course on Immunology and Infectious Disease at Lausanne, Switzerland. This course presents a unique opportunity to assemble the finest immunologists from the developing world. Before NEI's participation, ocular immunology had not been included in the course. In 1982, the course offered the opportunity for scientists to discuss various aspects of ocular autoregulation, ocular immunoregulation, and ocular parasitic disease. It is hoped that the course will interest re-

searchers because onchocerciasis, leprosy, and toxoplasmosis are major problems in these developing countries.

The NEI is cooperating with the U.S. Committee of the International Agency for the Prevention of Blindness in planning its Second General Assembly. Over 61 countries and 250 individual participants will gather in Bethesda, Maryland, October 24 through 28, 1982, for this global conference, which will be the largest gathering of experts on blindness prevention ever convened. The theme of the assembly, "New Horizons in Sight," reflects the fact that the IAPB's original goal--the creation of national committees throughout the world for the prevention of blindness--is almost fully achieved and that many of these committees have been successful in initiating sight conservation programs in their countries. At this assembly the results achieved by many of these programs will be evaluated, and the most successful ones identified as models for other countries to follow in the develop-

ment of their programs. It is hoped that by demonstrating the substantial progress achieved to date, this assembly may convince governments of developing countries that well-designed blindness prevention programs should be supported where they are needed. If this message is successfully conveyed, the chances are greater that the battle against preventable blindness worldwide can be won.

### **NIH Visiting Program and Health Scientist Exchange Programs**

The NEI continued to serve as an international center for research and research training in eye diseases. Thirty-six Visiting Scientists, Fellows, and other researchers from 17 different countries around the world participated in research projects at the NEI campus in Bethesda in FY 1982.



## **Chapter XIV**

### **National Institute of General Medical Sciences**

#### **Introduction**

The National Institute of General Medical Sciences (NIGMS) gives financial support for research and research training to a number of basic biomedical science disciplines that undergird the disease-specific initiatives of the categorical NIH Institutes.

#### **Extramural Programs**

The NIGMS accepts designated grant applications, which fall within its mission to support basic biomedical research, from principal investigators at appropriate institutions in countries other than the United States; and it funds those with the highest scientific merit. Eight such grants were funded during FY 1982 to principal investigators in four countries: Argen-

tina, Canada, Israel, and the United Kingdom.

The foreign grants were funded by four Institute programs, namely, the Cellular and Molecular Basis of Diseases Program, the Genetics Program, the Pharmacological Sciences Program, and the Physiology and Biomedical Engineering Program.

#### **International Conferences, Seminars, and Meetings**

The NIGMS joined other Institutes at the NIH to provide foreign travel funds for American and foreign scientists to participate in two international conferences: the Twelfth International Congress of Biochemistry, held in August 1982 at Perth, Australia; and the International Conference on Streptococcal Genetics, held in November 1981 at Sarasota, Florida.

# Chapter XV

## National Institute of Neurological and Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) serves as the unit of the NIH responsible for basic and clinical research on disorders of the nervous system and of human communication. Through its research grant program, application of P.L. 480, which permits use of U.S.-owned foreign currencies in specific countries and collaborative research projects engaging the NINCDS scientists and their foreign colleagues, the Institute maintains a continuing interaction with international neuroscientists. Because neurological and communicative disorders are major problems in virtually every country of the world, all nations stand to benefit from international research efforts and interchange of knowledge. Further, some of the neurological disorders vary in incidence and severity from country to country. The study of these variations and identification of their causes should lead to a clearer understanding of the causes of the disorders themselves. Therefore, the potential impact of international neuroscience research is great.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other

#### Country-to-Country Activities

In FY 1982, the NINCDS had a number of informal agreements in effect. In addition, the Institute began negotiations with the Government of Italy for epidemiological studies of stroke and the dementias.

In 1982, the NINCDS sponsored four P.L.-480 projects. Two of these projects were in Poland, and two were in Egypt. Both Polish projects concerned neuromuscular disorders, one being a study of the role of neurological cells in the processes of myelination and demyelination, and the other a study of the degree of muscle lesion in different disease conditions, as well as the connection between endocrine and muscle disturbances. The Polish groups, located at the

Medical Academy of Warsaw and at the Medical Academy in Poznan, have access to virtually all cases of neuromuscular disease in Poland and are a valuable international research resource.

The two remaining P.L.-480 projects were both in Egypt. One concerned perinatal screening of developmental malformations; the other was a study of the venoms of poisonous snakes. The perinatal screening project, in which over 100,000 patients in Cairo and Mansura have now been studied, has revealed a higher than expected incidence of spina bifida and anencephaly. Data from this project are undergoing a comprehensive analysis to discover the reasons for the higher incidence. The snake venom study, involving collection of venoms from North and East Africa as well as from Egypt, has resulted in publication of six scientific papers in journals outside Egypt and has put the Government of Egypt in a position to manufacture good anti-venins for North and Central Africa.

#### Activities With International Agencies

Since 1975, the NINCDS has been one of 13 WHO Collaborating Centers in the Neurosciences. These centers, positioned strategically throughout the world, further international research efforts on neurological disorders and initiate and demonstrate community programs for prevention and treatment of these disorders. Special emphasis is being given to the cerebrovascular disorders (stroke), the convulsive disorders (epilepsy), and the neurological and communicative disorders related to nutritional and developmental problems of children. The other 12 Collaborating Centers in the Neurosciences are:

- The Laboratoires d'Etudes et de Recherches Synthelabo, Paris, France
- The Arthur Vining Davis Center for Behavioral Neurobiology, The Salk Institute, San Diego, California
- The Montreal Neurological Institute, Montreal, Canada



- The Groupe Hospitalier de la Timone, Marseilles, France
- The Fundacion Instituto Neurologico de Colombia, Bogotá, Colombia
- The Clinique Neurologique, Dakar, Senegal
- The University of Ibadan, Ibadan, Nigeria
- The Institute of Neurology, The Academy of Medical Sciences of the U.S.S.R., Moscow, U.S.S.R.
- The Centre Medical Universitaire, Geneva, Switzerland
- The Instituto Nacional de Neurologia y Neurocirugia, Mexico City, Mexico
- The Shanghai First Medical College, Shanghai, China
- The Beijing Neurosurgical Institute, Beijing, China

Each center funds its own activities and includes collaborative research, publications for scientific information exchange, support of conferences and courses, advisory services, technical assistance, and training of new investigators.

As part of this effort, the NINCDS, the NIH Fogarty International Center, and WHO jointly sponsor an International Neurosciences Fellowship Program. This program provides men and women from developing countries with stipends for advanced training in the United States so that they can assume leadership roles in academic and public health careers in the neurosciences in their own countries. In 1982, the NINCDS supported five international neuroscience fellows from China, four at the NIH and one at the University of Minnesota Medical School.

### **The NIH Visiting Program**

During FY 1982, the NINCDS intramural program was host to 85 Visiting Scientists, Visiting Associates, and Visiting Fellows from 58 countries. Represented were Argentina, Australia, Austria, Bangladesh, Belgium, Bolivia, Brazil, Canada, Chile, China, Colombia, Czechoslovakia, Denmark, Egypt, Finland, France, the Federal Republic of Germany, Ghana, Greece, Guatemala, Guyana, Hong Kong, Hungary, India, Iran, Ireland, Israel, Italy, Jamaica, Japan, Korea, Luxembourg, Mexico, Nepal, the Netherlands, New Zealand, Nigeria, Norway, Pakistan, Panama, Peru, the Philippines, Poland, Portugal,

Sierra Leone, South Africa, Spain, Sri Lanka, Sweden, Switzerland, Turkey, the U.S.S.R., the United Kingdom, Uruguay, Venezuela, Yugoslavia, Zimbabwe, and Taiwan.

The contributions of these investigators add immeasurably to the strength and effectiveness of the NINCDS Intramural Program, and the experience and new knowledge they take back with them to their home countries strengthen the neurosciences around the world.

### **Extramural Programs**

NINCDS awarded 21 foreign research grants in FY 1982 to institutions in Canada, Israel, Italy, Mexico, New Zealand, Sweden, and the United Kingdom. These grants supported both clinical and basic research and have been awarded to outstanding investigators exploring problems of high priority in the United States and in their own countries.

The University of Western Ontario received the largest NINCDS foreign grant in 1982 for the gathering and analysis of data from approximately 60 U.S. and foreign medical centers on the effectiveness of a surgical procedure for preventing strokes. The procedure--known as the extracranial/intracranial bypass--involves grafting a scalp artery to an intracranial artery to improve blood supply. Although the technique is widely practiced, it is not statistically proven to be better than other forms of treatment. By 1983 the results of this study will be available to neurosurgeons and stroke specialists in all countries.

### **International Conferences, Seminars, and Meetings**

In 1981, the Institute provided some support for the World Federation of Neurology Meetings in Tokyo, Japan. Several staff members attended. In 1982, the First International Brain Research Organization World Congress on the Brain in Health and Disease was held in Lausanne, Switzerland. The NINCDS provided support for planning this meeting. In addition, the XII Symposium Neuroradiologicum--held in Washington, D.C., in 1982--was partially supported by an NINCDS grant and attracted visitors from many countries.

### **Intramural Programs and Activities**

Work continues on development of new anti-convulsant drugs, combining the efforts of pharmaceutical firms in Europe and Japan. Two promising drugs, one from Japan and one from France, are now being tested under NINCDS contracts. The NINCDS Epilepsy Branch con-

tinues to work with Epilepsy International to improve the use of anti-epileptic drugs. A team from the NINCDS Epilepsy Branch is working with the WHO Neurosciences Collaborating Center in Mexico to evaluate a protocol for studying the pharmacokinetics of anticonvulsant drugs in non-Caucasian populations, particularly in developing countries.

The NINCDS Laboratory of Central Nervous System Studies continues research on the slow, latent, virus-induced brain disorders such as

Creutzfeldt-Jakob disease and on Korean hemorrhagic disease with renal syndrome. In reference to the latter, scientists have demonstrated the presence of the causative agent in North American rodents.

A continual interchange occurs among NINCDS intramural and foreign scientists on topics of interest, not only through scientific meetings but also through visits to laboratories and consultations with scientists doing related work.



# Chapter XVI

## Warren G. Magnuson Clinical Center

### Introduction

The Warren G. Magnuson Clinical Center (CC) was authorized by Congress to provide the high-quality patient care necessary to conduct biomedical research. The 546-bed hospital has facilities and support services for nearly 1,000 physicians who conduct clinical research for 8 of the 11 NIH Institutes and for the National Institute of Mental Health. Since its establishment nearly 30 years ago, the CC has served as a prototype for many research hospitals. It was specially designed to place patient care facilities close to research laboratories to promote quick transfer of new findings of basic and clinical scientists to the treatment of patients. More than 4,000 patients are admitted annually (upon referral by their personal physicians); and in accordance with increasing emphasis on prevention and ambulatory health care, outpatients are now observed and treated at a newly opened ambulatory care research facility.

The CC ensures the highest possible level of medical care to each patient; provides optimal resources and facilities for clinical research; performs research on methods and systems involved in patient care and study; disseminates information to professionals and to the public relevant to clinical investigation; develops and maintains training programs in the techniques and ethics of biomedical and clinical research; and interacts with scientists and physicians, nationally and internationally, on such mutual problems of clinical research as policy, education, ethics, and priorities.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

A French-American-British (FAB) Cooperative Group is developing a uniform classification of acute leukemias and myeloproliferative syndromes that will be useful in the prognosis and treatment of patients with these diseases. The group is composed of seven bone

marrow morphologists: two from the United Kingdom, three from France, and two from the United States. The Chief of the CC Hematology Service is one of the U.S. representatives.

#### NIH Visiting Program and Health Scientist Exchange Programs

A Japanese expert consultant has begun a 2-year project to purify the NANB virus (described above) and to develop a NANB test system. This area is crucial to further clinical studies of this agent.

Development of assays to detect different agents for hepatitis and additional epidemiologic information should decrease the risk of hepatitis following blood transfusion and permit selection of low-risk blood donors for safer blood products.

The Clinical Center Blood Bank has been involved in several international collaborative research projects in the hepatitis area in FY 1982. The primary goals have been evaluation of data concerning posttransfusion hepatitis in different populations, collaborative efforts to identify markers for posttransfusion hepatitis, and exchange of scientific information and experience about posttransfusion hepatitis, a disease that has a significant worldwide distribution.

The risk of transmitting hepatitis through blood is affected by a variety of factors--social, economic, and ethnic. A cooperative study was undertaken to compare the frequency of hepatitis viral antigens and antibodies among blood donors in the U.S.S.R. and the United States. The results permit calculation of age and sex prevalence of hepatitis B and hepatitis A serologic markers for blood donors within and between each country, as well as comparison, on the same sera, of test methodologies in use in both countries.

No accepted assay is available for the agent that transmits non-A, non-B (NANB) hepatitis. A coded panel of NANB infectious sera and appropriate controls was distributed to investigators in the United Kingdom, France, the Federal Republic of Germany, and Costa Rica. Blood Bank investigators have been responsible for the collation and interpretation of results that have identified a candidate assay.

# Chapter XVII

## Division of Computer Research and Technology

### Introduction

Established in 1964, the Division of Computer Research and Technology (DCRT) was designed to make computational methods a tool for the NIH biomedical community. Over the years, the work of the Division has become an integral part of the conduct and management of NIH research programs. At the same time, the DCRT has grown to become the largest biomedical computing facility in the world. DCRT staff members continue to create still more powerful and useful systems. They continually seek new ways to bring computers, mathematics, and engineering into the service of science and to enhance administrative effectiveness.

### Summary of International Programs and Activities

#### Activities With International Agencies

In a study sponsored by WHO, the Data Management Branch collaborated with a researcher from Nigeria in creating a data base for examining the prevalence of major neurological diseases in that country.

#### Extramural Programs

DCRT staff members collaborated with scientists from foreign countries including Australia, Canada, China, France, Ghana, Greenland, Japan, Nigeria, and Singapore. Examples of these international collaborative activities include:

- Computer support for flow microfluorometry/cell sorters (Europe and Australia)
- Statistical research in clinical pathology (Belgium and Japan)
- Multivariate statistical analysis (Australia)

- Theory and measurement of intermolecular forces (Canada)
- Analysis of coupled transport and biochemical kinetics (France)
- Prevalence of major neurological diseases (Nigeria)

Other visitors to the DCRT throughout the year included foreign scientists from China, the Federal Republic of Germany, and the Republic of South Africa.

#### International Conferences, Seminars, and Meetings

The Division cosponsored, with the European Society of Cardiology and others, the annual conference on Computers in Cardiology. At this forum physicians, engineers, and computer scientists exchange information on the design of computer systems and their application to cardiology.

A delegation of foreign scientists attending the Sixth Annual Conference on Computers in Chemistry and Education came to visit DCRT for a briefing on the varied work of the Division. Countries represented by this group included Austria, Belgium, Canada, China, the Federal Republic of Germany, Finland, France, Hungary, Israel, Japan, Sudan, Switzerland, the United Kingdom, and the U.S.S.R.

#### Intramural Programs and Activities

The Data Management Branch is designing a system for the computerization of data on biomedical scientists and institutions in China. Officials at the FIC will use the system to brief NIH and non-NIH scientists interested in biomedical research in that country.

The Branch also designed a system that allows the FIC to maintain and query a data base that contains information on foreign scientists who are in the United States to perform health research.



An FIC Fellow in the Laboratory of Applied Studies of the DCRT has contributed to the theory of dynamic risk assessment in acute disease by creating very general, yet practical, methods for sequential analysis of time-dependent multivariant measurement vectors obtained during the course of a patient's illness. Combining these methods with discriminant function techniques enables daily reassessment of probable patient outcome. The procedures have been

applied successfully to patients under intensive care following myocardial infarction.

#### **NIH Visiting Program and Health Scientist Exchange Programs**

Three foreign scientists, two from Israel and one from Belgium, continued to work at the Division during FY 1982.

# Chapter XVIII

## Division of Research Resources

### Introduction

The Division of Research Resources (DRR) develops and supports a variety of multicategorical, interdisciplinary research resources essential to biomedical research. These resources are used by a broad spectrum of investigators to enhance their own effectiveness and that of their institutions in responding to and carrying out the mission of the National Institutes of Health. The DRR comprises five major programs: (1) General Clinical Research Centers, (2) Biotechnology Resources, (3) Minority Biomedical Research Support, (4) Biomedical Research Support, and (5) Animal Resources.

Of these, the Animal Resources Program (ARP) is the most involved in international activity. The ARP provides researchers with animals that are essential for studies on human disease processes and physiological systems. The ARP is also concerned with the study and preservation of animal populations in their natural environments. The ARP consists of two subprograms: the Primate Research Centers Program (PRCP) and the Laboratory Animal Sciences Program (LASP). The PRCP supports seven regional primate research centers and the LASP supports specialized animal models and colonies, as well as a variety of other animal resource projects. Several of these projects are conducted outside the United States.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

Of increasing international concern is the preservation of declining nonhuman resources to support biomedical research at a time of expanding agricultural and industrial development. To address this issue, the IXth Congress of the International Primatological Society was held August 8-13, 1982, in Atlanta, Georgia. It was hosted by the Yerkes Regional Primate Research Center and attended by over 700 scientists and other individuals interested in primatology research, including about 30 representatives from

10 countries that are original habitats for various species of nonhuman primates. Overall, the congress was considered highly successful and a number of publications related to primate conservation will result.

#### Extramural Programs

The Yerkes Primate Center, a grantee of the PRCP, provides support to the Kenyan Primate Center, Kenya, East Africa, for establishment of a base of information on African primate species (particularly the baboon in its native habitat); for exchange of information on these animals; and for research projects related to the survival of these animals in their native habitat.

The PRCP provides support through the Washington Regional Primate Research Center for Indonesian primate research activities at the Kutai Field Station. The orangutan, gibbon, and other primates native to this part of the world are endangered or threatened species whose habitats are rapidly being destroyed by industrial and agricultural development in Indonesia. This support is important for the development of information related to the survival of these species and the continued availability of these important species for use in biomedical research.

The LASP supports a project in northern India that focuses on population studies of nonhuman primates. This project, initiated in 1959 and supported by ARP since 1973, has provided data regarding population dynamics and demographic and reproductive parameters of a natural rhesus monkey population. One study group has increased 16.8 percent in numbers in the 4 years since the export ban on rhesus monkeys, compared with an increase of 16.5 percent in the 4 years prior to the ban. Since populations with good birth rates and low infant mortality rates can increase at the rate of 16 percent per year, the rhesus population could have been expected to increase at least 50 percent since the ban. The actual figures indicate that similar factors influenced the population both before and after the ban and that export per se has not been a dominant factor. Ongoing studies will provide data on the effects of habitat displacement, which is occurring with one study group, and the feasibility of intentional transplants and relo-



cation of breeding groups. Such information is necessary as a guide to conservation and management of rhesus monkeys and will be important in evaluating the potential supply of rhesus monkeys for biomedical research.

A second project supported by the LASP involves the study of important habitat features of West African rain forest primates. This project includes a detailed examination of the relationships between feeding behavior, specific ecological conditions, and social organization. It is

essentially a predictive study in which important variables such as foraging styles, diet selection, home range, group size patterns, population density, distribution, and social interaction are expected to relate in specific ways to ecological conditions. The information will be useful, not only to behaviorists, socio-ecologists, and botanists, but also to conservationists and those making decisions about the size of forest areas in Africa necessary to maintain wild populations of primates.

# Chapter XIX

## Division of Research Services

### Introduction

Through collaboration and cooperation with national and international organizations, the Division of Research Services (DRS) plans and conducts centralized programs of scientific, engineering, and technical services in support of biomedical research activities. Professional and technical staff members consult with research scientists during all stages of a research project on the development and use of essential products and services. DRS personnel provide specialized assistance and services in biomedical engineering and instrumentation design and development; research animal production, maintenance, procurement, and animal disease identification and control; provide biomedical library and translation services; and make available specialists in medical arts and photography.

The DRS is involved internationally in such activities as developing a primate supply program for biomedical research; establishing training programs in conservation and management of wild primates; supplying organizations and institutions throughout the world with genetically defined rodents as nuclei for colony development; sponsoring the development of methods for primate population studies and surveys; developing programs to train technicians in scientific instruments and to establish repair and maintenance centers in six universities in Egypt; and developing a regional program for repair and maintenance of hospital clinical care equipment in the eastern Caribbean countries of Barbados, St. Lucia, St. Vincent, Montserrat, St. Kitts, Antigua, and Dominica.

The DRS has detailed to the Department of State a senior staff member, who has been assigned to the U.S. Embassy in New Delhi, India, as the U.S. Scientific Attache and International Health Representative. In this assignment he assists the Scientific Counselor in all matters relating to U.S. scientific affairs in India with specific responsibility for representing, monitoring, and coordinating the program interests of the U.S. Department of Health and Human Services and other U.S. agencies engaged in health and health-related activities.

### Summary of International Programs and Activities

#### Bilateral Agreements and Other Country-to-Country Activities

##### Agreement with Japan on Cooperation in Research and Development in Science and Technology

In April 1980, a collaborative project in laboratory animal science was instituted as part of the U.S.-Japan Non-Energy Cooperative Agreement. The purpose of the project is to promote the exchange of information on laboratory animal models, the development and use of uniform international standards for research animals, and the exchange of information on other aspects of laboratory animal science. The DRS has responsibility for U.S. involvement in this project.

Initially, the purpose of the project was to develop information on quality control of laboratory animals. Several workshops on quality control provided material to be used in a series of U.S./Japan laboratory animal quality control manuals. In addition, representatives from both countries have actively participated in workshops on genetic and microbiological monitoring.

##### Egyptian Ministry of Health

On April 17, 1980, an agreement was signed between the Egyptian Ministry of Health and DHHS. Under a Special Foreign Currency Project, the Egyptian Ministry of Health, in cooperation with the Biomedical Engineering and Instrumentation Branch, National Institutes of Health, DHHS, will develop a pilot repair and maintenance center for medical equipment. This center will service a cross-section of Ministry of Health medical facilities in Giza. It is anticipated that the center, after suitable modifications, will serve as a model for a program in the repair and maintenance of medical equipment applicable nationwide in Egypt.

During 1980, the American Project Officer and the Egyptian Principal Investigator met to



develop an operating plan for the center and an implementation plan for the project. Project implementation began in 1981 with the training of center personnel--both in Egypt and the NIH--the purchase of equipment supplies for the center, and the construction of a building to house the center on the grounds of Hamwandia Hospital. The center became operational in 1982.

By the end of FY 1982, the center had developed repair capacity in excess of that required to service Hamwandia Hospital alone; therefore, consideration is being given to increasing the number of hospitals and clinics serviced by the center.

Under an interagency agreement with the National Science Foundation, the Biomedical Engineering and Instrumentation Branch, DRS, assisted five Egyptian universities in the development of repair and maintenance centers for scientific equipment. This project was carried out under an agreement between the USAID and the Egyptian Academy of Scientific Research and Technology providing for assistance "to help organize and direct the Egyptian scientific community toward dealing with the practical problems inhibiting economic development and social improvement."

#### Caribbean

Under a Participating Agency Service Agreement with USAID, the Biomedical Engineering and Instrumentation Branch is (1) participating in a joint effort with Project Hope to improve the repair and maintenance capability of the Jamaican Ministry of Health biomedical equipment repair facilities and develop a biomedical equipment maintenance program at the College of Arts, Science and Technology in Kingston and (2) developing a cooperative regional program for the maintenance hospital clinical care equipment for the islands of the eastern Caribbean. The program in the eastern Caribbean will be tailored to meet the individual needs of the countries involved and will make full use of existing repair capability, both in the private and in the public sectors. The implementation plan calls for the development of two repair centers within the region to provide repair services throughout the region. To date, this branch has made site visits to the countries involved to determine their repair and maintenance needs, purchased an inventory of basic maintenance tools and equipment for each of the islands, reviewed the capability of existing repair and maintenance personnel in the region, and selected personnel for training in instrument maintenance.

#### Activities with International Agencies

##### World Health Organization: Resource of Laboratory Rodents

The NIH genetic resource of laboratory rodents has been designated as a collaborating center for defined laboratory animals by WHO, and as an international nude mouse reference center by the International Council on Laboratory Animal Science. The resource maintains over 200 stocks and strains of genetically defined and monitored rodents and rabbits and serves as a source of breeding nuclei of animals used by NIH research investigators as well as by the international biomedical research community. Approximately 6,000 animals were supplied to domestic and foreign research institutions in FY 1982.

##### World Health Organization: Primate Supply Program

A contract has been established with WHO to develop an international primate supply program. WHO is to provide expert consultation and advisory assistance to the governments of countries interested in taking measures to ensure the continuing availability of nonhuman primates for use in biomedical research. This contract is intended to implement recommendations made by the Interagency Primate Steering Committee as outlined in the National Primate Plan.

The NIH has a critical interest in the continuing supply of nonhuman primates. Intramural research programs at the NIH use more nonhuman primates than any other government organization. In addition, NIH extramural research requires one-third of the total animals used for health-related programs. Another major user group is the pharmaceutical/biological industry, where nonhuman primates are required for the production and testing of drugs and biologic products that are licensed and controlled by the FDA. Because primate populations are rapidly declining, and because these animals are important to human, health-related needs, the objectives served by the WHO contract are of the utmost importance.

##### Pan American Health Organization

The Interagency Primate Steering Committee, through a contract with PAHO has developed projects to establish New World primate breeding centers and conservation programs in Latin

American countries. Although the majority of these countries imposed restrictions on the commercial export of nonhuman primates in 1973, they are interested in providing those species required for biomedical research through captive breeding and controlled wildlife management programs.

Specific objectives of the contract are:

- To provide expert consultants and advice to Latin American governments interested in developing primate programs as recommended by WHO;
- To assist in developing national programs of wild primate conservation and management to ensure the perpetuation of natural nonhuman primate resources; and
- To support development of primate breeding stations to produce species important to biomedical research under captive or semicaptive conditions.

The fully established Peruvian National Primate Project includes a breeding station in Iquitos, as well as field management activities. Marmosets and squirrel monkeys have been provided from this operation for use in U.S. biomedical activities since 1976.

An agreement was also established between PAHO and the Government of Colombia to develop a captive owl monkey breeding station at

Armero and to assist in ongoing conservation programs. Primate breeding and conservation programs have also been initiated in Brazil. These programs will eventually become self-supporting through funds received for primates made available for scientific use.

In addition to contract support, DRS staff provided consultive services in FY 1982 to several South American countries on matters related to primate conservation, breeding, and nutrition. These services are part of the overall cooperative effort to ensure the availability of nonhuman primate species as animal models for human disease.

### **NIH Visiting Program and Health Scientist Exchange Programs**

A Visiting Scientist from England was recruited to establish an NIH program in zeugmatography, a technique for medical diagnostic imagery based on the principles of nuclear magnetic resonance (NMR). Since his arrival in November 1977, he has conceived and designed an entirely new method for producing three-dimensional NMR images. Moreover, he has successfully tested several major components of the system, and its first images are expected within the next few months. In addition, since his arrival, he has made numerous significant contributions to the scientific literature of NMR imaging.



# Appendix

## Definitions of NIH International Program Activities

### Research Awards

#### Foreign Research Grants

The NIH supports research projects outside the United States only when they have met special criteria established for foreign grants. These criteria include the highest scientific merit and relevance to the program interests of the NIH as well as conformance with NIH, DHHS, and other U.S. policies.

#### Cooperative Agreement Awards

Cooperative agreement awards are noncompeting research grants to support collaborative projects between sponsoring Institutes and principal investigators, usually conducted under a formal protocol.

#### Core Grant to Gorgas Memorial Institute

A core grant to the Gorgas Memorial Institute/Gorgas Memorial Laboratory in Panama is appropriated through the budget of the FIC, NIH. The GML conducts research in tropical diseases of importance to Central America and the United States.

#### Domestic Grants With Foreign Components

A domestic grant with a foreign component is an NIH-financed grant with a domestic investigator in which a part of the grant is used to support research in a foreign country.

#### International Collaboration in Infectious Diseases

##### Research Awards

Under the International Collaboration in Infectious Diseases Research Program, emphasis is given to developing relationships between U.S. institutions and counterpart institutions abroad in infectious diseases research. The ICIDR Program was begun in 1979 when the Inter-

national Centers for Medical Research, which had existed from 1962, were phased out. In table A-1, the data for ICIDR awards are reported with other "Domestic Grants With Foreign Components." In tables A-2 and A-3, ICIDR awards are reported separately.

#### International Scientific Meetings

The NIH assists in the support of scientific meetings held to coordinate, exchange, and disseminate information when such activities are directed toward objectives clearly within the areas of NIH program interests. Activities reported include international components of those meetings supported under this research program area.

#### Special Foreign Currency (P.L. 480) Grants

The Special Foreign Currency Program, administered by the FIC, enables the NIH to support overseas activities that contribute to the advancement of health sciences in the United States. Funded by U.S.-owned local excess currency primarily derived from the sale of surplus U.S. agricultural commodities, these activities include biomedical research and the translation and dissemination of scientific literature. Funds for the Special Foreign Currency Program are appropriated to the Office of the Assistant Secretary for Health, DHHS, and awarded and administered by the NIH.

#### Foreign Contracts

Research contracts with institutions outside the United States must comply with the criteria prescribed for foreign grants.

#### Domestic Contracts With Foreign Components

A domestic contract with a foreign component is an NIH-financed contract with a domestic institution in which a part of the contract is used to support research in a foreign country.

## **Scientist Exchanges**

### **Visiting Fellows, Associates, Scientists**

The NIH Visiting Program offers talented scientists throughout the world the opportunity to share the research resources of the NIH. Through this program, distinguished scientists at all levels of their careers are invited to the NIH to receive further research experience and to conduct research in their biomedical specialties.

### **International Research Fellowships**

The FIC International Research Fellowship Program provides awards to foreign scientists in the formative stages of their careers to come to the United States for up to 2 years of advanced research training. Fellows are required to return to their respective home countries at the termination of their fellowships.

### **Scholars-in-Residence**

The FIC Scholars-in-Residence Program has been developed to facilitate the work of individual scholars and the exchange of ideas among scholars, distinguished science leaders, and science administrators. Scholars-in-Residence are nominated by NIH scientists and spend up to 10 months in residence at the NIH.

### **Senior International Fellowships**

The FIC Senior International Fellowship Program provides opportunities for established U.S. faculty members, who have demonstrated productive scholarship and achieved recognized stature in their profession, to go abroad to conduct collaborative research and to share their expertise. It is intended that this award be a career-enhancing educational experience with mutual benefits to both home and host institutions.

### **National Research Service Awards**

Under NIH National Research Service Awards, predoctoral, postdoctoral, and special fellowships to promote training for research in health-related sciences are granted each year to U.S. citizens, noncitizen nationals of the United

States, or persons who have been lawfully admitted to the United States for permanent residence. With acceptable justification, these fellowships may be taken at foreign institutions. Fellowships are not awarded for study leading to the M.D., D.D.S., D.V.M., or other applied science degree.

### **Foreign Work/Study Assignments**

The Foreign Work/Study Program involves overseas work assignments developed by NIH professionals not only to meet their own training and experience needs, but also to contribute to the domestic and/or international goals of the DHHS. Potential assignments are developed directly with foreign institutions, U.S. organizations having overseas installations, or other appropriate organizations that can provide a foreign work/study experience to fulfill program objectives.

### **International Travel**

International travel is defined as travel by NIH personnel, traveling under DHHS travel orders, to locations outside the United States, including Canada and Mexico, to attend international meetings and to participate in multilateral organization (e.g., WHO, PAHO) activities. This category also includes travel under bilateral exchanges.

### **BID Program Support**

#### **Bilateral Exchanges**

Bilateral exchanges not only contribute to advancement of biomedical and behavioral science for the benefit of health in the United States, but also serve the purposes of (1) overcoming social or political barriers (e.g., China, U.S.S.R.), (2) fostering sharing of technical resources and expertise (e.g., France, Israel, Japan), (3) drawing on unique resources or settings (e.g., India, Nigeria), and (4) furthering U.S. foreign policy objectives (e.g., Egypt, Kuwait). NIH participation is geared to scientific benefits to be derived. Funding, which is dependent on competition with other program needs, is derived from regular BID operating funds.



Figure A-1.--NIH international activities, funding by mechanism, FY 1982

(in millions of dollars)



FY 1982 Total for International Activities: \$62.1\*

\*Includes \$3.7 of "Other Funds" — i.e., not appropriated to NIH.

Figure A-2.--NIH international research and research training awards, FY 1973-82

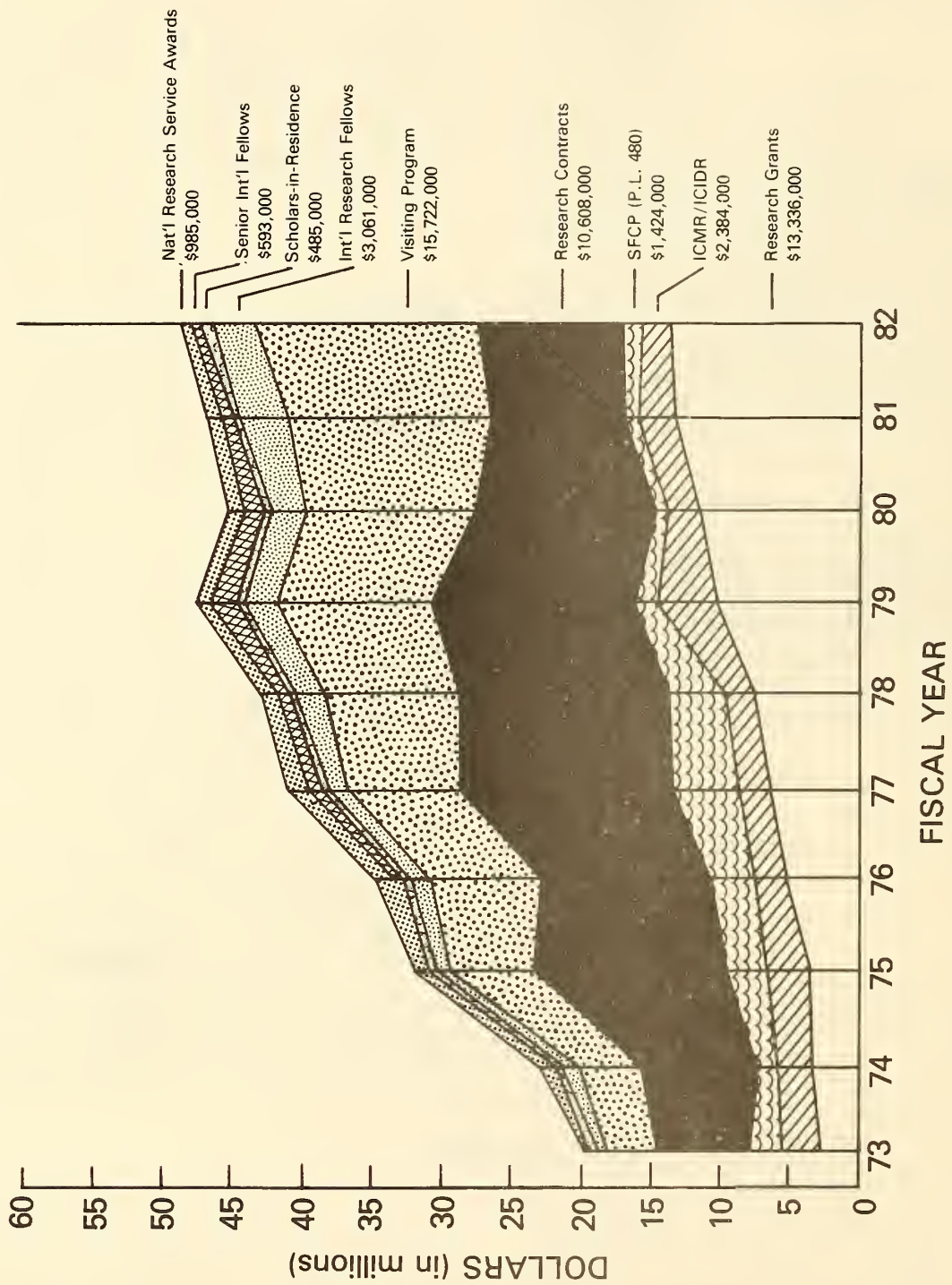




Figure A-3.--NIH international research and research training awards, FY 1973-82

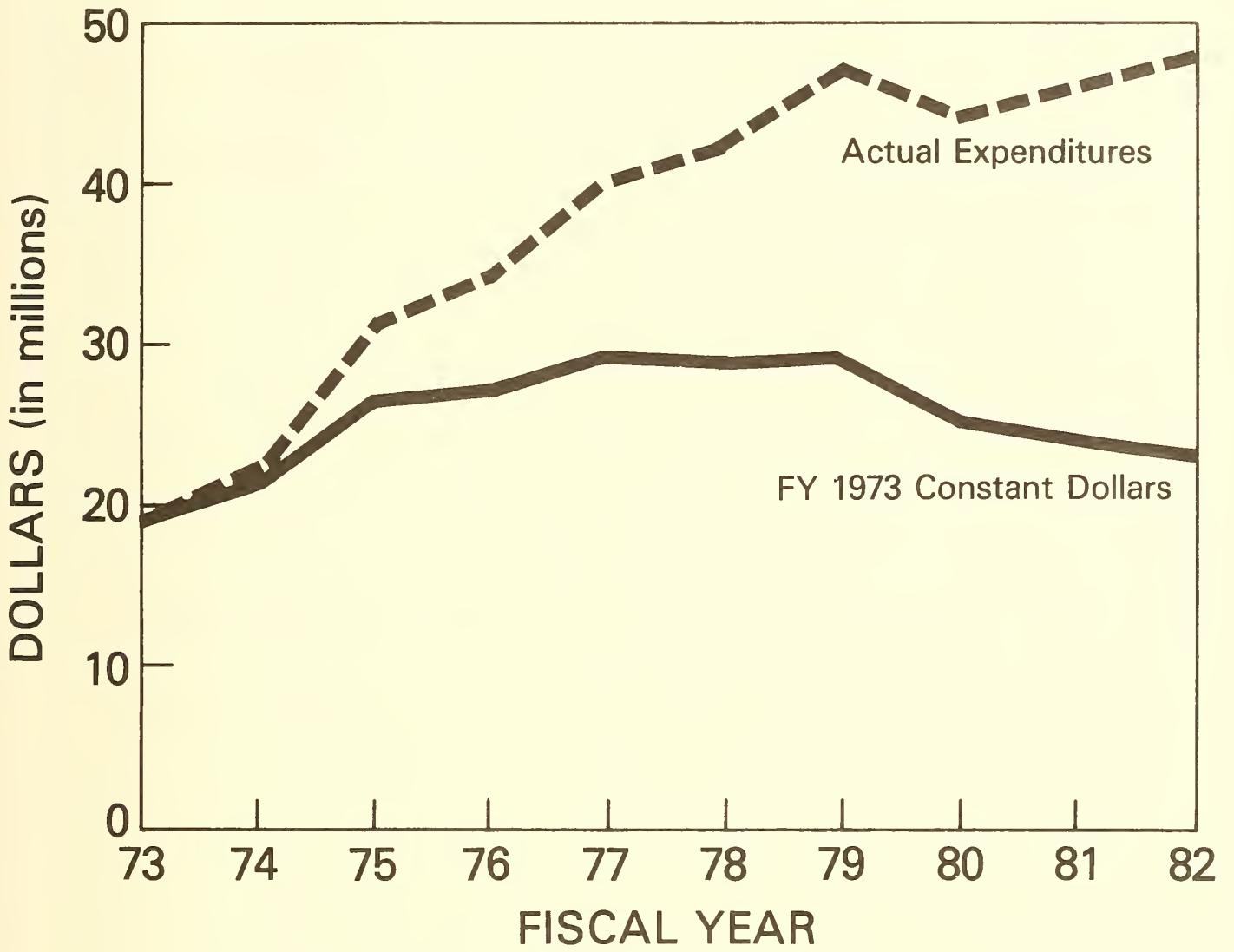


Table A-1.--Total expenditures for NIH international programs, by activity and BID, FY 1982  
(in thousands of dollars)

	OD	NCI	NHLBI	NIADDK	NLM	NIA	NIAID	NICHD	NIDR	NIEHS	NEI
Research awards											
Grants											
Foreign research grants	-	2,826	792	1,644	-	465	848	785	484	250	654
Cooperative agreement awards	-	1,196	-	37	-	-	-	-	-	692	-
Core grant to Gorgas Memorial Institute <sup>1</sup>	-	-	-	-	-	-	-	-	-	-	-
Domestic grants with foreign components <sup>2</sup>	-	1,009	110	47	-	201	2,271	422	-	3	68
International scientific meetings	-	99	231	54	-	14	44	15	98	-	-
Special Foreign Currency (P.L. 480) Grants <sup>3</sup>	-	927	46	11	5	-	285	68	-	-	58
Contracts											
Foreign contracts	197	5,959	1,566	222	49	14	2,909	258	-	272	-
Domestic contracts with foreign components	-	-	-	-	-	-	4	-	-	-	-
Scientist exchanges											
Foreign scientists in United States <sup>4</sup>											
Visiting Fellows, Associates, Scientists	-	5,616	867	2,772	12	505	1,150	1,054	775	648	413
International Research Fellowships	-	-	-	-	-	-	-	-	-	-	-
Scholars-in-Residence	-	-	-	-	-	-	-	-	-	-	-
U.S. scientists abroad											
Senior International Fellowships	-	-	-	-	-	-	-	-	-	-	-
National Research Service Awards	-	34	110	73	-	-	86	23	-	-	60
Foreign work/study assignments	-	125	-	31	-	-	-	80	-	-	-
International travel											
International meetings	9	243	91	109	10	18	53	6	56	26	17
Multilateral organization activities	4	48	10	2	3	8	34	20	-	39	9
Bilateral exchanges	4	54	13	1	-	-	26	5	-	26	13
Other	-	131	14	61	3	-	91	30	3	36	4
BID program support											
Bilateral exchanges	-	457	620	27	-	29	179	-	-	59	20
Other program support	15	331	252	50	185	26	86	-	11	82	15
Totals <sup>5</sup>	229	19,055	4,722	5,141	267	1,280	8,065	2,766	1,427	2,160	1,331



Table A-1.--Continued

	NIGMS	NINCDS	CC	CRT	FIC	RR	RS	Totals	NIH funds	Other funds	Funds expended in U.S., abroad
<b>Research awards</b>											
<b>Grants</b>											
Foreign research grants	744	1,921	-	-	-	-	-	11,411	11,411	-	X
Cooperative agreement awards	-	-	-	-	-	-	-	1,925	1,925	-	X
Core grant to Gorgas Memorial Institute <sup>1</sup>	-	-	-	1,692	-	-	-	1,692	1,692	-	X
Domestic grants with foreign components <sup>2</sup>	16	-	-	-	-	-	-	4,174	4,174	-	X
International scientific meetings	29	57	7	3	406	22	-	1,077	1,077	-	X
Special Foreign Currency (P.L. 480) Grants <sup>3</sup>	-	24	-	-	-	-	-	1,424	-	(1,424)	X
<b>Contracts</b>											
Foreign contracts	-	232	-	-	-	-	355	12,012	10,608	(1,404)	X
Domestic contracts with foreign components	-	-	-	-	-	-	-	4	4	-	X
<b>Scientist exchanges</b>											
<b>Foreign scientists in United States<sup>4</sup></b>											
Visiting Fellows, Associates, Scientists	17	1,633	87	53	-	-	119	15,722	15,722	-	X
International Research Fellowships	-	-	-	-	3,061	-	-	3,061	3,061	-	X
Scholars-in-Residence	-	-	-	-	485	-	-	485	485	-	X
<b>U.S. scientists abroad</b>											
Senior International Fellowships	-	-	-	-	593	-	-	593	593	-	X
National Research Service Awards	365	235	-	-	-	-	-	985	985	-	X
Foreign work/study assignments	-	-	-	-	-	-	-	236	236	-	X
<b>International travel</b>											
International meetings	4	139	1	4	-	-	5	792	368	(424)	X
Multilateral organization activities	-	30	-	-	-	-	11	216	42	(175)	X
Bilateral exchanges	-	-	-	-	-11	-	40	194	75	(118)	X
Other	-	-	1	2	3	1	1	381	159	(222)	X
<b>BID program support</b>											
Bilateral exchanges	-	-	-	-	297	-	7	1,694	1,694	-	X
Other program support	-	190	46	-	2,624	-	70	3,983	3,983	-	X
<b>Totals<sup>5</sup></b>	<b>1,175</b>	<b>4,461</b>	<b>142</b>	<b>62</b>	<b>9,172</b>	<b>23</b>	<b>588</b>	<b>62,061</b>	<b>58,294</b>	<b>(3,767)</b>	

1 Core Grant to Gorgas Memorial Institute/Gorgas Memorial Laboratory (Panama) is appropriated through the budget of the Fogarty International Center, NIH.  
 2 The category "Domestic Grants With Foreign Components" now includes the International Collaboration in Infectious Diseases Research (ICIDR) Program, which was formerly reported in the category of "Special Foreign Grants." The dollar amounts for the foreign components of domestic grants have been estimated.

3 P.L. 480 funds are appropriated to the Office of the Assistant Secretary for DHHS and awarded and administered by the NIH.

4 Numbers of Guest Researchers are presented in Table 2. Because these researchers are supported by home institutions and other sources, the NIH has no record of dollars expended.

5 Totals may not add because of rounding.

Table A-2.--NIH international research and research training awards  
by country/area and mechanism,<sup>1</sup> FY 1982

(in thousands of dollars)

Country/area	Total		Research grants		Cooperative agreements		ICIDR		SFCP (P.L. 480)		Research contracts	
	number	amount	number	amount	number	amount	number	amount	number	amount	number	amount
Argentina	24	452	4	118	-	-	-	-	-	-	-	-
Australia	45	1,731	21	1,301	-	-	-	-	-	-	-	-
Austria	5	79	-	-	-	-	-	-	-	-	-	-
Bangladesh	3	40	-	-	-	-	-	-	-	-	-	-
Belgium	18	357	3	133	-	-	-	-	-	-	-	-
Bolivia	1	40	-	-	-	-	-	-	-	-	-	-
Brazil	13	1,243	-	-	-	-	3	1,053	-	-	-	-
Canada	122	7,409	60	4,311	11	472	-	-	-	-	14	1,981
Chile	8	151	-	-	-	-	-	-	-	-	-	-
China	38	750	-	-	-	-	-	-	-	-	1	195
Colombia	2	465	-	-	-	-	1	447	-	-	-	-
Denmark	12	247	2	104	-	-	-	-	-	-	-	-
Egypt	7	1,041	-	-	-	-	-	-	-	-	1	945
Finland	24	532	6	250	-	-	-	-	-	-	1	28
France	42	698	3	73	-	-	-	-	-	-	-	-
Germany, F.R.	21	637	2	130	-	-	-	-	-	-	1	258
Ghana	2	26	-	-	-	-	-	-	-	-	1	13
Greece	10	170	-	-	-	-	-	-	-	-	-	-
Guatemala	1	18	-	-	-	-	-	-	-	-	-	-
Guyana	-	-	-	-	-	-	-	-	-	-	-	-
Hong Kong	3	75	-	-	-	-	-	-	-	-	-	-
Hungary	11	132	-	-	-	-	-	-	-	-	-	-
India	121	3,070	-	-	-	-	1	52	12	1,283	-	-
Iran	2	30	-	-	-	-	-	-	-	-	-	-
Ireland	6	134	-	-	-	-	-	-	-	-	-	-
Israel	103	4,419	38	2,130	-	-	-	-	-	-	7	1,262
Italy	94	1,575	3	82	-	-	-	-	-	-	1	145
Jamaica	2	15	-	-	-	-	-	-	-	-	-	-
Japan	204	3,493	3	28	-	-	-	-	-	-	3	492
Korea	12	173	1	12	-	-	-	-	-	-	-	-
Lebanon	2	30	-	-	-	-	-	-	-	-	-	-
Luxembourg	3	47	-	-	-	-	-	-	-	-	-	-
Mexico	13	213	2	68	-	-	1	36	-	-	-	-
Nepal	1	24	-	-	-	-	-	-	-	-	-	-
Netherlands	22	494	1	145	-	-	-	-	-	-	2	73
New Zealand	9	182	1	58	-	-	-	-	-	-	-	-
Nigeria	8	114	-	-	-	-	-	-	-	-	-	-
Norway	5	94	-	-	-	-	-	-	-	-	-	-
Pakistan	1	6	-	-	-	-	-	-	-	-	-	-
Panama	-	-	-	-	-	-	-	-	-	-	-	-
Peru	3	57	-	-	-	-	-	-	-	-	-	-
Philippines	3	71	-	-	-	-	-	-	-	-	-	-
Poland	22	431	-	-	-	-	-	-	-	-	-	-
Portugal	2	20	-	-	-	-	-	-	-	-	-	-
Romania	1	25	1	25	-	-	-	-	-	-	-	-
Sierra Leone	2	21	-	-	-	-	-	-	-	-	-	-
South Africa	4	133	-	-	1	42	-	-	-	-	-	-
Spain	23	454	1	35	-	-	-	-	-	-	-	-
Sri Lanka	2	18	-	-	-	-	-	-	-	-	-	-
Sudan	2	382	-	-	-	-	1	355	-	-	-	-
Sweden	52	1,773	19	1,228	-	-	-	-	-	-	-	-



Table A-2.--Continued

Country/area	Visiting Program		Int'l Research Fellows		Guest Researchers number	Senior Int'l Fellows		Nat'l Research Service Awards	
	number	amount	number	amount		number	amount	number	amount
Argentina	14	194	6	140	(7)	-	-	-	-
Australia	13	250	9	153	(11)	1	9	1	18
Austria	4	53	1	26	(7)	-	-	-	-
Bangladesh	3	40	-	-	(1)	-	-	-	-
Belgium	10	129	5	95	(6)	-	-	-	-
Bolivia	1	40	-	-	-	-	-	-	-
Brazil	3	45	7	145	(7)	-	-	-	-
Canada	27	485	-	-	(16)	1	26	9	134
Chile	2	19	5	117	-	1	15	-	-
China	31	437	6	118	(22)	-	-	-	-
Colombia	1	18	-	-	(1)	-	-	-	-
Denmark	6	57	4	86	(5)	-	-	-	-
Egypt	5	71	1	25	(2)	-	-	-	-
Finland	6	62	11	192	(2)	-	-	-	-
France	24	354	9	167	(22)	1	13	5	91
Germany, F.R.	14	181	-	-	(29)	1	16	3	52
Ghana	1	13	-	-	-	-	-	-	-
Greece	10	170	-	-	(3)	-	-	-	-
Guatemala	1	18	-	-	-	-	-	-	-
Guyana	-	-	-	-	(2)	-	-	-	-
Hong Kong	3	75	-	-	(1)	-	-	-	-
Hungary	11	132	-	-	(2)	-	-	-	-
India	102	1,623	6	112	(15)	-	-	-	-
Iran	2	30	-	-	-	-	-	-	-
Ireland	1	18	5	116	(1)	-	-	-	-
Israel	47	785	5	114	(13)	3	75	3	53
Italy	80	1,140	7	155	(49)	3	53	-	-
Jamaica	2	15	-	-	-	-	-	-	-
Japan	192	2,827	5	132	(51)	-	-	1	14
Korea	10	134	1	27	(5)	-	-	-	-
Lebanon	1	5	1	25	-	-	-	-	-
Luxembourg	3	47	-	-	(1)	-	-	-	-
Mexico	6	39	4	70	(2)	-	-	-	-
Nepal	1	24	-	-	-	-	-	-	-
Netherlands	16	221	3	55	(6)	-	-	-	-
New Zealand	5	54	3	70	-	-	-	-	-
Nigeria	4	47	4	64	(2)	-	-	-	-
Norway	1	17	4	76	(5)	-	-	-	-
Pakistan	1	6	-	-	-	-	-	-	-
Panama	-	-	-	-	(1)	-	-	-	-
Peru	1	18	2	39	(2)	-	-	-	-
Philippines	3	71	-	-	(1)	-	-	-	-
Poland	18	327	4	104	(5)	-	-	-	-
Portugal	2	20	-	-	(1)	-	-	-	-
Romania	-	-	-	-	-	-	-	-	-
Sierra Leone	2	21	-	-	-	-	-	-	-
South Africa	3	91	-	-	-	-	-	-	-
Spain	13	243	9	176	(4)	-	-	-	-
Sri Lanka	2	18	-	-	(1)	-	-	-	-
Sudan	-	-	1	27	-	-	-	-	-
Sweden	17	245	11	210	(9)	2	30	3	60

Table A-2.--Continued

Country/area	Total		Research grants		Cooperative agreements		ICIDR		SFCP (P.L. 480)		Research contracts	
	number	amount	number	amount	number	amount	number	amount	number	amount	number	amount
Switzerland	34	607	4	199	-	-	-	-	-	-	-	-
Tanzania	2	51	-	-	-	-	-	-	-	-	1	50
Thailand	2	470	1	29	-	-	1	441	-	-	-	-
Turkey	2	42	-	-	-	-	-	-	-	-	-	-
United Kingdom	134	3,497	18	774	-	-	-	-	-	-	8	943
United States	146	3,177	-	-	-	-	-	-	-	-	-	-
Uruguay	1	24	-	-	-	-	-	-	-	-	-	-
U.S.S.R.	-	-	-	-	-	-	-	-	-	-	-	-
Venezuela	2	51	-	-	-	-	-	-	-	-	1	13
Yugoslavia	17	352	1	46	-	-	-	-	7	141	-	-
Zimbabwe	1	17	-	-	-	-	-	-	-	-	-	-
Taiwan	10	168	-	-	-	-	-	-	-	-	-	-
Stateless	-	-	-	-	-	-	-	-	-	-	-	-
Unspecified	9	118	-	-	-	-	-	-	-	-	-	-
International Organizations												
EORTC	2	428	-	-	1	215	-	-	-	-	-1	213
IARC	5	2,884	-	-	1	504	-	-	-	-	-4	2,380
IUAC	3	609	1	127	-	-	-	-	-	-	2	482
PAHO	4	1,080	1	5	-	-	-	-	-	-	3	1,074
WHO	2	752	-	-	1	692	-	-	-	-	-1	60
Total	1,512	48,113	197	11,411	15	1,925	8	2,384	19	1,424	53	10,608



Table A-2.--Continued

Country/area	Visiting Program		Int'l Research Fellows		Guest Researchers number	Senior Int'l Fellows		Nat'l Research Service Awards	
	number	amount	number	amount		number	amount	number	amount
Switzerland	17	190	5	55	(12)	4	97	4	66
Tanzania	1	1	-	-	-	-	-	-	-
Thailand	-	-	-	-	-	-	-	-	-
Turkey	2	42	-	-	(2)	-	-	-	-
United Kingdom	70	1,070	5	69	(16)	12	260	21	381
United States	146	3,177	-	-	(9)	-	-	-	-
Uruguay	-	-	1	24	(2)	-	-	-	-
U.S.S.R.	-	-	-	-	(2)	-	-	-	-
Venezuela	1	38	-	-	(4)	-	-	-	-
Yugoslavia	8	143	1	22	(2)	-	-	-	-
Zimbabwe	1	17	-	-	-	-	-	-	-
Taiwan	8	114	2	55	(2)	-	-	-	-
Stateless	-	-	-	-	(1)	-	-	-	-
Unspecified	-	-	-	-	-	-	-	9	118
International Organizations									
EORTC	-	-	-	-	-	-	-	-	-
IARC	-	-	-	-	-	-	-	-	-
IUAC	-	-	-	-	-	-	-	-	-
PAHO	-	-	-	-	-	-	-	-	-
WHO	-	-	-	-	-	-	-	-	-
Total	979	15,722	153	3,061	(372)	29	593	59	985

NOTE: Numbers in parentheses are not added into totals.  
Totals may not add due to rounding.

1 Table A-2 includes only those categories in table I that constitute research and research training awards.

Table A-3.--NIH international research and research training awards, FY 1947-82<sup>1</sup>

(in thousands of dollars)

Fiscal Year	Total		Research grants		ICMR/ICIDR <sup>2</sup>		SFCP (P.L. 480)		Training grants		Research contracts	
	number	amount	number	amount	number	amount	number	amount	number	amount	number	amount
1947	19	179	5	130	-	-	-	-	-	-	-	-
1948	37	346	11	253	-	-	-	-	-	-	-	-
1949	79	347	16	130	-	-	-	-	-	-	-	-
1950	68	391	20	219	-	-	-	-	-	-	-	-
1951	83	412	28	210	-	-	-	-	-	-	-	-
1952	85	495	22	257	-	-	-	-	-	-	-	-
1953	79	495	24	245	-	-	-	-	-	-	-	-
1954	88	497	15	145	-	-	-	-	-	-	-	-
1955	88	470	14	111	-	-	-	-	-	-	-	-
1956	116	683	18	190	-	-	-	-	-	-	-	-
1957	224	1,808	61	824	-	-	-	-	1	13	-	-
1958	318	2,777	92	1,307	-	-	-	-	1	17	-	-
1959	495	5,425	170	2,997	-	-	-	-	2	30	-	-
1960	749	8,492	307	5,249	-	-	-	-	3	39	-	-
1961	1,064	12,692	563	8,999	-	-	-	-	7	251	3	90
1962	1,416	22,770	811	13,410	5	2,093	20	2,765	13	380	2	118
1963	1,707	24,067	981	14,956	7	2,093	16	1,517	16	536	8	181
1964	1,645	25,590	932	13,759	6	2,484	19	3,328	17	544	5	182
1965	1,540	23,514	801	11,467	6	2,491	25	3,026	22	615	13	429
1966	1,494	21,653	718	10,010	5	2,423	22	2,182	18	559	22	867
1967	1,218	20,068	624	8,509	5	2,360	27	3,559	15	506	29	901
1968	1,066	20,525	480	6,424	5	2,360	42	5,459	15	506	27	1,037
1969	950	19,985	325	4,481	5	2,294	44	7,312	16	449	35	1,325
1970	756	15,267	170	2,968	4	2,070	39	4,503	11	187	32	1,369
1971	736	21,844	120	2,489	5	2,285	79	10,149	4	46	34	1,805
1972	850	19,762	113	2,449	4	2,399	24	2,894	-	-	41	2,319
1973	782	19,874	116	2,905	4	2,244	21	2,706	-	-	65	5,337
1974	861	23,020	119	3,360	4	2,360	13	1,544	-	-	86	6,508
1975	1,002	31,867	130	3,917	4	2,411	24	3,257	-	-	105	8,381
1976	1,235	34,457	138	5,128	4	2,400	18	2,934	-	-	120	13,790
1977	1,304	40,719	149	6,532	4	2,400	25	4,484	-	-	134	12,525
1978	1,404	42,829	162	7,502	4	2,117	16	4,199	-	-	135	15,173
1979	1,452	47,333	191	10,042	13	4,699	9	1,298	-	-	139	15,107
1980	1,485	45,179	206	11,139	10	2,756	9	612	-	-	117	14,759
1981	1,548	46,622	237	13,223	10	2,585	20	911	-	-	93	12,932
1982	1,532	48,598	212*	13,336*	8	2,384	19	1,424	-	-	61	9,672
											53	10,608



Table A-3.--Continued

Fiscal Year	Visiting Program number amount	Int'l Research Fellows number amount	Scholars-in-Residence number amount	Guest Researchers number	Senior Int'l Fellows number amount	Nat'l Research Service Awards number amount
1947	-	13	-	-	-	1
1948	-	23	-	-	-	12
1949	-	55	-	-	-	3
1950	1	36	-	-	-	8
1951	5	37	-	-	-	11
1952	7	36	-	-	-	13
1953	6	13	-	-	-	20
1954	17	2	-	-	-	36
1955	26	-	-	-	-	54
1956	42	-	-	-	-	48
1957	76	-	-	-	-	56
1958	110	16	-	-	-	86
1959	128	67	-	-	-	99
1960	138	68	-	-	-	128
1961	149	92	-	-	-	834
1962	190	90	-	-	-	230
1963	200	172	-	-	-	251
1964	179	183	-	-	-	279
1965	156	166	-	-	-	310
1966	139	166	-	-	-	296
1967	129	176	-	-	-	342
1968	149	151	-	-	-	397
1969	138	168	-	-	-	211
1970	178	137	-	-	-	188
1971	188	130	-	-	-	1,724
1972	259	163	-	-	-	1,504
1973	290	110	-	-	-	222
1974	351	127	5	130	-	185
1975	494	107	5	119	-	1,101
1976	679	137	6	141	-	1,314
1977	740	126	8	182	-	1,806
1978	804	128	12	228	-	214
1979	830	134	13	219	-	143
1980	909	132	8	163	-	129
1981	976	136	8	150	-	115
1982	979	153	16	180	42	75
			12	159	50	1,050
			12	205	64	823
			11	229	75	1,065
			20	266	52	1,009
			18	355	32	1,227
			20	372	29	673
						593

\* Includes cooperative agreement awards

1 Table A-3 includes only those categories in table A-1 that constitute research and research training awards.

2 International Centers for Medical Research (ICMRs) existed from FY 1962 through FY 1979, when program changes resulted in the phasing out of ICMRs and the initiation of grants under the International Collaboration in Infectious Diseases Research (ICIDR) Program.

## Index by Country

- Argentina, 19, 25, 41, 42, 44, 58, 59, 86, 96, 97, 105  
 Australia, 2, 7, 14, 19, 20, 25, 41, 58-60, 63-65, 67, 72, 74, 86, 91, 97, 103, 105, 108  
 Austria, 19, 38, 41, 65, 71, 91, 105, 108  
 Bangladesh, 62, 65, 74, 84, 86, 105  
 Belgium, 19, 25, 41, 59, 65, 71, 86, 97, 105, 108, 109  
 Bolivia, 105  
 Brazil, 2, 19, 25, 37, 41, 42, 44, 45, 58, 69, 72, 74-76, 84, 86, 91, 96, 105, 114  
 Canada, 2, 7, 20, 39, 41, 44, 45, 46, 58, 59, 65, 67, 71, 72, 86, 91, 96, 97, 101, 103-105, 108, 116  
 Chile, 19, 20, 42, 44, 58, 72, 105  
 China, 3, 4, 6, 7, 11, 14, 15, 19, 20, 25, 26, 29, 35, 36, 43, 45-47, 59, 62, 65, 72, 74, 76, 84-87, 89, 93, 97, 105, 108, 116  
 Colombia, 6, 41, 42, 44, 67, 74, 84, 86, 105, 114  
 Denmark, 14, 19, 41, 58, 86, 105  
 Dominican Republic, 7, 73, 77, 86  
 Egypt, 2, 4, 20, 22, 24, 25, 29, 35, 36, 41, 43, 47, 67, 68, 72, 74, 77, 86, 93, 104, 105, 112, 113, 116  
 Finland, 1, 19, 25, 41, 44, 47, 63, 64, 72, 96, 97, 105, 108  
 France, 7, 14, 18-22, 25, 30, 35-37, 41, 43, 46-48, 59-61, 63-65, 67, 71, 72, 74, 85, 86, 91, 97, 104, 105, 107, 108, 116  
 Germany, 11, 14, 18, 20, 21, 25, 29, 31, 35, 36, 41, 43, 45, 46, 48, 59, 64, 65, 67, 72, 75, 78, 85, 86, 96, 97, 105, 107, 108  
 Ghana, 41, 65, 74, 78, 86, 105, 108  
 Greece, 25, 41, 59, 65, 72, 105  
 Guyana, 105  
 Hong Kong, 7, 15, 59, 71, 105  
 Hungary, 21, 22, 25, 29, 31, 35, 36, 41, 65, 72, 86, 97, 105, 108  
 Iceland, 41  
 India, 2, 6, 14, 19, 22-25, 41, 49, 59, 62, 65, 67, 68, 72, 74, 78, 79, 84, 86, 87, 97, 99, 100, 105, 110, 112, 116  
 Iran, 41, 105  
 Ireland, 19, 59, 105  
 Israel, 2, 14, 19, 20, 25, 39, 41, 43, 44, 45, 49, 50, 58, 59, 63-65, 67, 71, 72, 74, 79, 86, 89, 91, 97, 103, 105, 108, 109, 116  
 Italy, 2, 14, 19, 20, 25, 26, 29, 32, 35, 36, 41, 43, 46, 50, 59, 64, 65, 67, 72, 79, 86, 94-96, 104, 105  
 Jamaica, 45, 58, 59, 105  
 Japan, 2, 3, 5-7, 15, 19, 25, 32, 33, 35, 36, 41, 43, 46, 50, 51, 59-62, 65, 67, 72, 74, 78-80, 85, 86, 88, 91, 94, 97, 100, 105, 108, 112, 116  
 Kenya, 6, 25, 41, 84, 110  
 Korea, 19, 41, 59, 65, 86, 91, 97, 105  
 Kuwait, 1, 45, 51, 74, 116  
 Lebanon, 19, 86  
 Luxembourg, 105  
 Mexico, 6, 19, 25, 26, 41, 42, 44, 45, 58, 67, 71, 74, 80, 82, 84, 86, 91, 97, 105, 106, 116  
 Nepal, 105  
 Netherlands, 19, 41, 59, 64, 65, 74, 80, 81, 84-86, 96, 97, 105  
 New Zealand, 7, 19, 41, 59, 65, 72, 91, 97, 105  
 Nigeria, 1, 6, 19, 25, 41, 51, 65, 74, 81, 84, 86, 88, 90, 105, 108, 116  
 Norway, 19, 41, 52, 59, 89, 105  
 Pakistan, 16, 22, 23, 25, 65, 81, 84, 105  
 Panama, 11, 26, 27, 74, 81, 86, 115  
 Peru, 6, 19, 41, 42, 44, 105  
 Philippines, 6, 7, 41, 59, 86, 88, 105  
 Poland, 3, 18, 19, 22-25, 29, 33, 35, 36, 41, 45, 46, 52, 59, 65, 67, 68, 72, 74, 88, 97, 104, 105  
 Portugal, 28, 65, 105  
 P.R.C., 29, 41, 46, 47, 75, 76, 93  
 Romania, 18, 21, 22, 25, 59, 96  
 Senegal, 25, 105  
 Sierra Leone, 74, 81, 86, 105  
 Singapore, 15, 108  
 South Africa, 15, 41, 65, 67, 81, 86, 105, 108  
 Spain, 19, 25, 41, 52, 65, 82, 105  
 Sri Lanka, 41, 72, 82, 105  
 Sudan, 19, 74, 82, 108  
 Sweden, 2, 14-16, 18-20, 41, 52, 59, 63, 65-67, 72, 74, 86, 89, 91, 97, 101, 105  
 Switzerland, 18-21, 37, 39, 41, 59, 65, 67, 72, 74, 85, 86, 97, 100, 101, 105, 108  
 Tanzania, 41, 43  
 Thailand, 41, 58, 62, 74, 76, 84  
 Turkey, 41, 59, 72, 105  
 U.S.S.R., 5, 18, 21, 22, 25, 28, 34-36, 41, 43, 45, 46, 53-57, 61, 63, 71, 72, 82, 85, 86, 94, 95, 100, 105, 107, 108, 116  
 United Kingdom, 2, 19, 20, 41, 59, 62, 64-67, 74, 84, 86, 103, 105, 107, 108, 1-7, 11, 13-15, 19, 21-37, 39, 43, 45-50, 52-59, 62-65, 68, 70, 71  
 United States, 73, 74, 76, 80, 84, 85, 87-91, 93, 94, 24, 99, 100, 103, 105, 107, 108, 110, 115, 116  
 Uruguay, 19, 41, 42, 44, 105  
 Venezuela, 6, 25, 41, 42, 57, 74, 86, 105  
 West Indies, 11, 19  
 Yugoslavia, 18, 19, 21-23, 25, 41, 58, 64, 65, 67, 72, 88, 97  
 Zambia, 41  
 Zimbabwe, 25, 65, 105  
 Taiwan, 7, 15, 19, 41, 59, 86, 97, 105



## Index by Research Area

- Aged, aging, 1, 7, 24, 52, 53, 58, 64, 70-72, 76, 101
- Allergy and infectious diseases  
Allergy, 1, 20, 73, 76  
Communicable disease, 83  
Immunology, 16, 22, 23, 26, 30, 31, 33-35, 37, 40, 56, 71, 74-78, 80, 82-85, 91, 101  
Infectious disease, 23, 80, 83, 84, 101
- Arthritis and skeletal diseases, 5, 21, 61, 63
- Cancer, 1-5, 15, 16, 21, 23, 25, 27-44, 51, 72, 76, 88, 93, 94
- Cardiovascular, pulmonary, and blood systems  
Anemia, including sickle cell anemia, 5, 17, 59, 61  
Blood, 1, 4-6, 13, 15, 17, 19, 24, 27, 31, 45-53, 55-60, 62, 64, 72, 81, 105, 107  
Cardiovascular/cardiovascular disease, 1, 5-7, 23, 25, 26, 45-53, 55, 57-59  
Coronary/coronary disease, 6, 7, 13, 45, 46, 49-52, 54, 55, 57-59  
Heart, 1, 5-7, 13, 15, 45-47, 49-59  
Hypertension, 6, 7, 13, 23, 45-49, 51, 52, 55-60, 64  
Lung, 1, 15, 28, 29, 32, 33, 43, 44, 45-47, 60, 93, 96, 97
- Clinical trials, 31-33, 41, 43, 46, 59, 82, 101
- Dental/Oral health, 1, 90, 91
- Diabetes, 5, 17, 19-21, 59, 61, 63, 64
- Endocrinology, 14, 40, 63, 89
- Environmental health, including occupational health, 2, 23, 93-95
- Epidemiology, 15, 17, 25, 27, 29-32, 35, 37, 39, 40, 43, 44, 47, 48, 53, 56, 59, 64, 73, 77-79, 81, 82, 85, 88, 89, 101
- Eye/vision, including glaucoma, 2, 13, 15, 17, 22, 24, 61, 62, 99-102
- Genetics, growth, and reproductive studies  
Child health, 7, 23, 87  
Family planning, 87  
Genetics, 5, 7, 16, 35, 40, 49, 51, 56, 64, 72, 75, 76, 83, 87, 89, 91, 94, 95, 97, 103  
Growth, 4, 16, 33, 38, 44, 54, 62, 87, 89, 93  
Human development, 7, 71, 87
- Hepatic, renal, and digestive systems  
Digestive diseases, 61  
Kidney, 5, 19, 31, 61, 63, 64, 68, 72, 82, 106  
Liver, 3-5, 29, 32, 34, 44, 65, 97
- Information sciences  
Information systems, 58, 66, 69, 82, 101  
Library, 24, 36, 37, 39, 66-69, 97, 112
- Metabolic diseases/metabolism, 30, 32, 50, 53-55, 62-65, 72, 82, 96, 97
- Neurological disorders and stroke  
Epilepsy, 6, 104-106  
Neuroepidemiology, 6  
Neurological disorders, 104  
Stroke, 2, 6, 13, 50, 51, 59, 60, 104, 105
- Nutrition, 15, 29, 44, 45-47, 51, 59-62, 64, 71, 87, 88, 90, 96, 99, 114
- Prevention, 1-3, 5, 13, 15, 24, 26, 28, 31-33, 35, 37, 40, 43-47, 49, 51, 52, 54, 58, 64, 73, 77, 78, 87, 90, 93, 99-102, 104







NIH LIBRARY



3 1496 00178 8929